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Research Article

Early prognosis of unstable angina patients with positive *Helicobacter pylori* IgG values

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Abstract

Background: Coronary atherosclerosis has been proven to be a chronic inflammatory disorder and various infectious agents like *H. pylori* have been proposed to be playing important role in initiation and progression of the atherosclerotic lesions.
Aim: To study the prognosis of the unstable angina patients who have positive *H. pylori* IgG values after following for a period of 30 days.

Materials and Methods: Patients with the clinical and the ECG features suggestive of unstable angina admitted at the Kasturba Medical college hospitals who were positive for *H. pylori* IgG values were followed up for a period of 30 days. These were study subjects. Controls had unstable angina and negative *H. pylori* IgG values. Study was carried out over 1 year.
Results and data analysis: There were a total of 46 cases and 40 controls in the study. The mean age among the cases was 56.50 years (SD 10.72 yrs) and 57.2 years (SD 10.48 yrs) in controls. Fisher's Exact test and one way ANOVA were used to compare distribution of risk factors and outcomes. There was no significant difference in the distribution of risk factors for coronary artery disease among two groups. ESR values& total leucocyte counts of the cases were higher. There was no significant difference in the outcome among the cases compared to the controls in any of the study end points.
Conclusions: he early prognosis of the patients of unstable angina with positive *H. pylori* IgG values is not significantly different from those with negative *H. pylori* IgG values.

Keywords: Unstable angina;early prognosis; *H. pylori* IgG

1. Introduction

Coronary atherosclerosis is a chronic inflammatory disorder, initiated and driven on by the recruitment and activation of inflammatory cells in the vascular intima, and has been linked with persistent bacterial or viral infections[1,2]. Epidemiological studies have shown increased prevalence of cardiovascular diseases in patients with serological evidence of infection by intracellular pathogens such as cytomegalovirus, herpes simplex virus, *chlamydia pneumoniae* and *helicobacter pylori* among many pathogens. These organisms are reported to be associated with the pathogenesis of the cardiovascular diseases. By the same mechanisms, *helicobacter pylori* is likely to be associated with the short term as well as long term prognosis of the cardiovascular diseases as well. But this aspect has not been studied till now. Our study is an

effort to understand the role of *helicobacter pylori* on the prognosis of cardiovascular disease events.

2. Materials and Methods

2.1 Sampling Method : Study sample was based on period based sampling. Patients who were positive for IgG *H. pylori* were taken as study subjects and similar number of patients who were negative for IgG *H. pylori* were taken as study controls.

2.2 Inclusion Criteria: Patients with the clinical and the ECG features suggestive of unstable angina admitted who were ***positive*** for *H. pylori* IgG values were followed up for a period of 30 days. These were study subjects. Controls were the patients with clinical and the ECG features suggestive of unstable angina admitted at the Kasturba Medical College hospitals who were ***negative*** for *H. pylori* IgG values. They were also followed up for a period of 30 days.

2.3 Exclusion Criteria: Patients who did not give consent to be part of the study. Patients who were not willing for follow up visits for subsequent 1 month.

Both the cases and the controls were evaluated by the following parameters.

1) Clinical Evaluation.

2) ECG

3) Chest X ray

4) Echocardiography

5) Cardiac enzymes: CPK-MB, TROP-T if needed over the following period of 30 days, they were evaluated for the development of adverse cardiac events like

a) Recurrent angina

b) Myocardial infarction

c) Heart failure

d) Death

The study was carried over a period of 1 year.

Definition of Unstable angina[3]

The angina pectoris or equivalent ischemic discomfort with at least one of the three features

(1) It occurs at rest (or with minimal exertion) usually lasting more than 10 minutes.

(2) It is severe and of new onset (that is within the prior 4 to 6 weeks), and/or

(3) It occurs with a crescendo pattern (that is distinctly more severe, prolonged, or frequent than previously.

2.4 Statistical Methods: For the analysis of data, the SPSS-PC (Statistical Package for Social Sciences) was used. The mean and proportions were used for each continuous variable like age, total leukocyte count, ESR. For comparing mean values of cases and controls of various measures, like total leucocyte count and ESR, one-way ANOVA was used. Fisher's Exact test was used to compare distribution of risk factors like hypertension, diabetes among the cases and the controls and to compare the outcome among *H. pylori* positive and *H. pylori* negative subjects.

3. Results and Data analysis

Our study involved following up of the cases presenting with the features of unstable angina attending the Kasturba Medical College hospitals for 1 month. The study was carried over a period of 1 year. A total of 86 cases of unstable angina-diagnosed by clinical history and evaluated by complete blood counts, ESR, ECG and IgG *H. pylori* by ELISA method were followed up. The patients were regularly followed up for next 1 month and noted for the development of nonfatal myocardial infarction, cardiac failure and death. The patients undergoing coronary angiogram and revascularization were noted. Few of the patients had sudden cardiac death during the study period. The patients were put into the cases and the control group based on the titres of IgG *H. pylori* by ELISA. Those patients with IgG *H. pylori* titres of more than 40 EU/ml were taken as positive- i.e. **cases** and those with titres less than 40 EU/ml were taken as negative- i.e**. controls**. We had a total of 46 cases and 40 controls in the study. This included 51 males and 35 females [table1]. All the patients were anticoagulated with heparin on admission and were on aspirin during the follow-up period.

Table 1: Study subjects according to Gender

Gender	Frequency	Percent
Male	51	59.3
Female	35	40.7
Total	86	100

The mean age among the cases was 56.50 years (SD 10.72 yrs). The mean age among the controls was 57.2 years (SD 10.48 yrs) and maximum number of patients were in less than 50 years age group [table 2]. The youngest among the **cases** was 36 year old, oldest being 77 years old. Among the **controls**, youngest was 39 year old and 77 year aged being the oldest.

Table 2: **Age Distribution of Subjects in the Study**

Age Group	*H. pylori* +	*H. pylori* –
< 50 years	14	12
50–60 years	12	10
60–70 years	13	11
>70 years	8	6

There was no significant difference in the distribution of risk factors for coronary artery disease like hypertension [Table 3], diabetes [Table 4], past history of ischemic heart disease [Table 5], type A personality [Table 6], smoking [Table 7], alcohol consumption [Table 8] among the cases compared to the controls.

Table 3: Hypertension among the Study and Control Groups

IgG *H. pylori*	HTN		Total
	Yes	No	
Positive	24	22	46
Negative	22	18	40
Total	46	40	86

P value: 0.793

Table 4: Diabetes Mellitus among the Study and Control Groups

IgG H. pylori	DM		Total
	Yes	No	
Positive	26	20	46
Negative	25	15	40
Total	51	35	86

Fisher's exact test; *P* value: .574

Table 5: IHD among the Study and Control Groups

IgG *H. pylori*	IHD		Total
	Yes	No	
Positive	17	29	46
Negative	14	26	40
Total	31	55	86

Fisher's exact test; *P* value: 0.850

Table 6: Type A Personality among the Study and Control Groups

IgG *H. pylori*	Type-A Personality		Total
	Yes	No	
Positive	16	30	46
Negative	13	27	40
Total	29	57	86

Fisher's exact test; *P* value: 0.823

Table 7: Smoking among the Study and Control Groups

IgG *H. pylori*	Smoking		Total
	Yes	No	
Positive	17	29	46
Negative	14	26	40
Total	31	55	86

Fisher's exact test; *P* value: 0.850

Table 8: Alcohol Intake among the Study and Control Groups

IgG *H. pylori*	Alcohol		Total
	Yes	No	
Positive	13	33	46
Negative	10	30	40
Total	23	63	86

Fisher's exact test; *P* value: 0.733

Table 9: Total Leucocyte Count and ESR among Cases and Controls

	Study Group	No of Patients	Mean	S.D	P Value
Total leucocyte count	Cases	46	9415.73	783.75	0.009
	controls	40	5506.75	520.5	
ESR	Cases	46	23.32	7.794	0.010
	controls	40	12.6	5.196	

Three patients each among cases and the controls developed non-fatal myocardial infarction during the study period [Table 10]. One patient each among both the groups developed cardiac failure [Table 11]. Two cases and three controls underwent coronary revascularization procedure [Table 12]. 2 cases and controls had sudden cardiac death during the period [Table 13]. Among the cases, after the follow up period, five patients had composite outcome, compared with controls where three had composite outcome (i.e. more than one of the clinical study end points mentioned above).There was no statistically significant difference in the outcome among the cases compared to the controls in any of the study end points.

Table 10: Association between the Presence of *H. pylori* and the Occurrence of Non-Fatal MI

IgG *H. pylori*	Non-Fatal MI		Total
	Yes	No	
Positive	2	44	46
Negative	0	40	40
Total	2	84	86

Fisher's Exact Test *P* value: 0.497

Table 11: Association between the Presence of *H. pylori* and the Occurrence of Heart Failure

IgG *H. pylori*	Heart Failure		Total
	Yes	No	
Positive	0	46	46
Negative	2	38	40
Total	2	84	86

Fisher's exact test; *P* value: 0.2

Table 12: Association between the Presence of *H. pylori* and Need of Revascularization

IgG *H. pylori*	Revascularization		Total
	Yes	No	
Positive	3	43	46
Negative	2	38	40
Total	5	81	86

Fisher's exact test; *P* value: 1.000

Table 13: Association between *H. pylori* and Occurrence of Death

IgG *H. pylori*	Death		Total
	Yes	No	
Positive	2	44	46
Negative	2	38	40
Total	4	82	86

Fisher's exact test; *P* value: 0.637

Analysis showed significant difference in the ESR values and total leucocyte counts of the cases and that of the controls probably indicating contribution of infection in pathogenesis of unstable angina [Table 9].

4. Discussion

The incidence of the cardiovascular diseases has been increasing all over the world and studies are being conducted all over to understand the reasons for this increasing trend. Cardiovascular diseases have been proposed to be associated with chronic infections since long and the increasing trend of the cardiovascular diseases, is at least in part, probably related to the infectious etiology. Several organisms have been proposed to have causal relationship with acute coronary syndromes. *Helicobacter pylori, Chlamydia pneumoniae, Mycoplasma pneumoniae, Haemophilus* influenza are some of these organisms. The association between *H. pylori* infection and coronary artery disease was described by Mendel *et al*. in 1994 and has further been tested by several studies[4,5,6,7,8,9,10]. Our study was conducted because of the conflicting results available from the study results published from different parts of world and also because the lack of studies in India till now testing the effect of *H. pylori* seropositivity on the prognosis of the patients with unstable angina. The primary end points of our study, recurrent angina, myocardial infarction, heart failure and death were studied in unstable angina patients with and without *H. pylori* seropositivity for a period of 28 days. There was no significant difference in any of the outcomes between the study groups. In other words, the early prognosis of unstable angina patients with *H. pylori* seropositivity was not different from those with *H. pylori* seronegativity.

The relation between *H. pylori* infection and cardiovascular diseases has been studied in many of the studies. Several studies support pathogenic link between *H. pylori* infection and coronary atherosclerosis. *H. pylori* is probably directly involved in pathogenesis of coronary heart disease because the DNA of *H. pylori* has been found in coronary arteries of individuals with coronary artery disease[11]. Infectious agents like *H. pylori* are likely involved not only in the initiation of the atherosclerosis, but also in the progression of the atherosclerosis as well. This has been proved by a study by Espinola-Klein *et al*., who showed significant association between infectious burden and the extent of atherosclerosis and also that in individuals with advanced atherosclerosis, the future risk of death is increased by the number of infectious

pathogens. Study by Niccoli *et al*. also support the association between CagA-positive *H. pylori* infection and coronary atherosclerotic burden[12]. The higher infectious burden in individuals with coronary artery disease has also been supported by an Iranian study[13]. So, association of *H. pylori* in atherosclerosis is logically expected to be associated with worse prognosis in acute coronary events. But this was not the case in our study and early prognosis in unstable angina was un affected by *H. pylori* seropositivity. Probably long term prognosis is influenced to a greater extent by *H. pylori* seropositivity.

H. pylori, because of the pathogenetic mechanism in atherosclerosis, is likely to be related to causation of unstable angina as well as myocardial infarction. Study by Miyazaki *et al*[14] and Seyed Mohammad Alavi *et al*[15] found a significant link between *H. pylori* infection and acute coronary syndrome. A study by Khodaii *et al*., [16] El Marshad *et al*. [17] showed an association between Acute Myocardial Infarction and *H. pylori* seropositivity. A Meta analysis by Franceschi F *et al*. suggests that in a subset of patients with unstable angina, an intense immune response against CagA-positive *H. pylori* strains might be critical to precipitate coronary instability mediated by antigen mimicry between CagA antigen and a protein contained in coronary atherosclerotic plaques[9]. But we did not observe significantly increased occurrence of myocardial infarction in subgroup of unstable angina patients with *H. pylori* seropositivity in our study during the one month follow up period.

But, there has been no consensus about the role of infectious agents in either causation or progression of cardiovascular diseases in all studies. A Canadian study was conducted to assess the role of *C. Pneumoniae, CMV, Adenovirus, Hepatitis A* and *H. pylori* in the development of atherosclerosis. This study found association between heart disease and *C. Pneumoniae* only but not with *H.pylori*[18]. Similarly, several others studies also have reported lack of association between Acute coronary syndromes and *H. pylori* infection[19,20,21,22]. Rahime Eskandarian *et al.* in a prospective study showed that *H. pylori* infection has no effect on short term prognosis of patients with ACS[23]. The same result has been observed in our study as well.

The role of infectious diseases in cardiovascular diseases has been tested in several major trials by looking for the prognosis after administering antibiotics to the individuals with acute coronary syndromes. WIZARD (Weekly Intervention with Zithromax for Atherosclerosis and Related Disorder) study [24] failed to find a long term benefit of administering Azithromycin for individuals with stable coronary artery disease, serologic evidence of *C. Pneumoniae* and past history of myocardial infarction. The ineffectiveness of antibiotics for prevention of secondary cardiovascular events has also been shown in ACES,[25] PROVE IT-TIMI[26] and AZACS[27] trials. But STAMINA[28] trial found that antibiotic treatment significantly reduces adverse cardiac events in patients with acute coronary syndromes, but this was independent of *H. pylori* or *C. pneumoniae* seropositivity.

There is some important link between the infectious diseases and the acute coronary syndromes as evident from the several studies quoted above, but this probably does not affect the early prognosis, which has been reflected by our study. So, the infectious agents like *H. pylori* may be related to the pathogenesis rather than outcome of coronary artery diseases. There is need to rethink and revise hypothesis and research strategies related to the role of infectious agents in coronary artery diseases. There is strong need to conduct research about pro-atherogenic mechanisms of infections in order to give boost for preventive cardiology. Only then there is possibility of discovering novel anti-infective agents and vaccines which will have positive impact in preventing ever increasing catastrophic cardiac coronary events all over the world.

5. Conclusions

The early prognosis of the patients of unstable angina with positive *Helicobacter pylori* IgG values is not significantly different from those with negative *Helicobacter pylori* IgG values.

Long term studies are needed to study the prognosis of unstable angina patients with *Helicobacter pylori* infection.

6. Limitation of Study

Angiography could not be performed on all the patients because of financial constraints, which might have helped in understanding impact of *H. pylori* sero-positivity on the extent of atherosclerosis, in addition to the prognosis.

References

1. Patel P, Mendall MA, Carrington D, Strachan DP , Leatham E, Molineaux *et al.* Association of *Helicobacter pylori* and

Chlamydia pneumoniae infections with coronary heart disease and cardiovascular risk factors. *BMJ* 1995; 311: 711-715.

2. Libby P, Egan D, Skarlatos S. Roles of infectious agents in atherosclerosis and restenosis: an assessment of the evidence and need for future research. *Circulation* 1997; 96: 4095-98.
3. E Braunwald, RH Jones, DB Mark, J Brown, L Brown, MD Cheitlin, CA Concannon, M Cowan, C Edwards and V Fuster. Diagnosing and managing unstable angina. Agency for Health Care Policy and Research. *Circulation* 1994; 90:613-622.
4. Danesh,Y Wong, M Ward, J Muir: chronic infection with *Helicobacter pylori, Chlamydia pneumoniae* or *Cytomegalovirus*: population based study of coronary heart disease. *Heart* 1999; 81: 245-247.
5. John Danesh, Rhodes scholar, Richard Peto: Risk factors for coronary heart disease and infection with *Helicobacter pylori*; meta-analysis of 18 studies. *BMJ* 1998; 316: 1130-1132.
6. Altannavch Ts, Roubalova K, Broz J, Hruba D, Andel M. Serological markers of *Chlamydia pneumoniae, cytomegalovirus* and *Helicobacter pylori* infection in diabetic and non-diabetic patients with unstable angina pectoris. Cent *Eur J Public Health* 2003; 11: 102-106.
7. Prasad A, Zhu J, Halcox JP, Waclawiw MA, Epstein SE, Quyyumi AA. Predisposition to atherosclerosis by infections: role of endothelial dysfunction. *Circulation* 2002; 106:184-90.
8. Singh RK, McMohan AD, Patel H, Packard CJ, Rathbone BJ, Samani NJ. Prospective analysis of the association of infection with Cag A bearing strains of *Helicobacter pylori* and coronary heart disease. *Heart* 2002; 88:436.
9. Franceschi F, Sepulveda AR, Gasbarrini A, Pola P, Silveri NG, Gasbarrini G *et al.* Cross reactivity of anti Cag A antibodies with vascular wall antigens; possible pathogenic link between *Helicobacter pylori* infection and atherosclerosis. *Circulation* 2002; 106: 4304.
10. Franceschi F, Niccoli G, Ferrante G, Gasbarrini A, Baldi A, Candelli M *et al.* CagA antigen of *Helicobacter pylori* and coronary instability: insight from a clinico-pathological study and a meta-analysis of 4241 cases. *Atherosclerosis* 2009; 202: 535-42.
11. Kowaski M, Rees W, Konturek PC, Grove R, Scheffold T *et al.* Detection of *H. pylori* specific DNA in human atheromatous coronary arteries and its association to prior myocardial infarction and unstable angina. *Dig Liver Dis* 2002; 34: 398-402.
12. Niccoli G, Franceschi F, Cosentino N, Giupponi B, De Marco G, Merra G *et al*. Coronary atherosclerotic burden in patients with infection by CagA-positive strains of *Helicobacter pylori*. *Coron Artery Dis* 2010; 21: 217-221.
13. Jafarzadeh A, Nemati M, Tahmasbi M, Ahmadi P, Rezayati MT, Sayadi AR. The association between infection burden in Iranian patients with acute myocardial infarction and unstable angina. *Acta Med Indones* 2011; 43:105-11.
14. Miyazaki M, Babazono A, Kadowaki K, Kato M, Takata T, Une H. Is *Helicobacter pylori* infection a risk factor for acute coronary syndromes? *J Infect* 2006; 52: 86-91.
15. Seyed Mohammad Alavi, Seyed Mohammad Hasan Adel, Alireza Rajabzadeh. Relationship between the serologic status of *helicobacter pylori* with the presence of unstable angina. Pak J Med Sci 2008; 24: 29-32.
16. Khodaii Z, Vakili H, Hosain, Ghaderian SM, Najar RA, Panah AS. Association of *Helicobacter pylori* infection with acute myocardial infarction. *Coron Artery Dis* 2011; 22: 6–11.
17. El-Mashad N, El-Emshaty WM, Arfat MS, Koura BA, Metwally SS. Relation of Cag-A-positive *Helicobacter pylori* strain and some inflammatory markers in patients with ischemic heart diseases. *Egypt J Immunol* 2009; 16:39-47.
18. Smeija M, Cronin L, Levine M, Goldsmith CH, Yusuf S, Mahony JB. Previous exposure to *Chlamydia Pneumoniae, Helicobacter pylori* and other infections in Canadian patients with ischemic heart disease. *Can J Cardiol* 2002; 17:270-6.
19. Wald NJ, Law MR, Morris JK, Bagnall AM. *Helicobacter pylori* infection and mortality from ischemic heart disease, negative results from a large, prospective study. *BMJ* 1997; 315: 1199-1201.

20. Collizzi C, Rizzello V, Angiolillo DJ, Liuzzo G, Ginnetti F, Monaco C *et al. In vitro* hyperreactivity to lipopolysaccharide in patients with history of unstable angina is not associated with seropositivity for *Cytomegalovirus, Helicobacter pylori* and *Chlamydia pneumoniae. Cardiologia* 1999; 44: 377-80.

21. Osserwaarde JM, Feskens EJ, De Vries A, Vallinga CE, Kromhout D. *Chlamydia pneumoniae* is a risk factor for coronary heart disease in symptom free elderly men but *Helicobacter pylori* and *cytomegalovirus* are not. *Epidemiol Infect* 1998; 120: 93-99.

22. Christodoulou DK, Milionis HJ, Pappa P, Katsanos KH, Sigounas D, Floretin M *et al.* Association of *Helicobacter pylori* infection with cardiovascular disease—Is it just a myth? *Euro J Intern Med* 2011; 22: 191-194.

23. R Eskandarian , S Moosavi , M Babai , J Toussy *et al.* Impact of *helicobacter pylori* on prognosis of patients with acute coronary syndrome. *ARYA* 2005; 1: 164-169**.**

24. **O**'Connor CM, Dunne MW, Pfeifer MA, Muhlestein JB, Yao L, Gupta S *et al.* Azithromycin for the secondary prevention of coronary heart disease events: the WIZARD study: a randomized controlled trial. *JAMA* 2003; 290: 1459–1466.

25. Grayston JT, Kronmal RA, Jackson LA, Parisi AF, Muhlestein JB, Cohen JD Parisi *et al*. Azithromycin for the Secondary Prevention of Coronary Events. *N Engl J Med* 2005; 352:1637-1645.

26. Cannon CP, McCabe CH, Belder R, Breen J, Braunwald E. Design of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trial *Am J Cardiol* 2002; 89:860-861.

27. Cercek B, Shah PK, Noc M. et al. Effect of short-term treatment with azithromycin on recurrent ischaemic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomized controlled trial. *Lancet* 2003; 361: 809-813.

28. Stone AF, Mendall MA, Kaski JC, Edger TM, Risley P, Poloniecki J *et al.* Effect of treatment of *Chlamydia pneumoniae* and *Helicobacter pylori* on markers of inflammation and cardiac events in patients with acute coronary syndromes: South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina (STAMINA). *Circulation* 2002; 106:1219-23.