

Helicobacter Pylori Seropositivity and Acute Myocardial Infarction

* **Wathiq K. Abdul-Gafour** *M.B.Ch.B., D.M., CABM*

** **Haitham I Baqir** *MB.ChB, PhD* *** **Riyadh S Al-Raubyee** *M.B.Ch.B., CABM*

Abstract

Background: Acute myocardial infarction (AMI) is one of the most common diagnoses in hospitalized patients. The stimulus that initiates the acute inflammatory process in AMI has not been identified. Conventional risk factors account only for approximately half of the patients with clinically apparent atherosclerosis which can lead to AMI. Recently a potential link between infectious agents and atherosclerosis has been suggested

Objective: To find a possible association between *Helicobacter pylori* (*H. Pylori*) infection and AMI.

Method: We studied the prevalence of *anti-H. pylori* antibodies in 94 patients who were admitted with the diagnosis of AMI and a

similar number of healthy individuals who were age and sex matched. This was done using ELISA technique.

Results: Overall prevalence of anti-*H. pylori* antibodies in patients with AMI was 82.9% whereas the prevalence in the control group was 78.7%. This difference yielded an odd ratio of 1.317. Chi square test shows that this difference was insignificant statistically (p-value 0.458)

Conclusion: We feel that our results do not support the hypothesis which stated that chronic infection with *H. pylori* is a major risk factor for AMI.

Key words: *H. pylori* seropositivity, acute myocardial infarction, Atherosclerosis

Al – Kindy Col Med J 2011; Vol. 7 No. 2 P: 9-15

Introduction:

Acute myocardial infarction (AMI) is one of the most common diagnoses in hospitalized patients in industrialized countries. AMI usually occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously affected by atherosclerosis. In most cases, AMI occurs when the surface of an atherosclerotic plaque becomes disrupted (exposing its contents to the blood) and conditions (local or systemic) favor thrombogenesis⁽¹⁾. Plaque rupture most frequently occurs in lipid-laden plaques with an endothelial cap weakened by internal collagenase (metalloproteinase) activity derived primarily from macrophages. These macrophages are recruited to the plaque from blood monocytes responding to inflammatory mediators and adhesion molecules⁽²⁾. The culprit coronary artery eventually becomes occluded by a thrombus containing platelet aggregates and fibrin strands⁽¹⁾. The stimulus that initiates the acute inflammatory process in AMI has not been identified^(3,4). Conventional risk factors, including hyperlipidemia,

hypertension, diabetes, tobacco use, sex, and family history of premature vascular disease, account only for approximately half of the patients with clinically apparent atherosclerosis. Recently a potential link between infectious agents and atherosclerosis has been suggested⁽⁵⁾. The pathological changes underlying occlusive vascular diseases show considerable overlap with those caused by a range of infections. Particular viral and bacterial pathogens have long been suspected of playing a part, directly or indirectly, in the process leading to atherosclerosis⁽⁶⁾. Infectious agents that have been linked to coronary heart disease (CHD) on epidemiological, clinical and pathogenic grounds include *Helicobacter pylori* (*H.pylori*), *Chlamydia pneumoniae*, and cytomegalovirus^(7,8). *Chlamydia pneumoniae*, cytomegalovirus, and *H.pylori* have been identified within human atherosclerotic lesions, and antibodies against *Chlamydia* heat shock proteins can cross-react against heat shock proteins produced by endothelium, resulting in endothelial damage and accelerated atherosclerosis. Antibodies to *Chlamydia*, cytomegal-

ovirus, and H.pylori are found more often in patients with atherosclerosis than in control subjects^(3,9). Chlamydia pneumoniae has been detected in various atheromatous vessels including coronary arteries but not often in healthy arteries⁽⁴⁾. H.pylori DNA has been detected in the coronary arteries only in sporadic occasions⁽¹⁰⁾. Potential mechanism in Chlamydia pneumoniae infection may result from direct vessel wall colonization which may damage the vessel directly or indirectly by initiating immunological responses. In other cases, the effect may simply be that of enhancing the preexisting chronic inflammatory response of the body to standard risk factors such as hyperlipidemia. Even though the infectious agent may not directly infect the vessel wall, it may perform its critical role from a far. Chronic infection may also influence preexisting plague by enhancing T-cell activation or other inflammatory responses that may participate in the de-stabilization of the intimal capillary. Chronic infection may play a role in the initiation, progression or de-stabilization of atherosclerotic plaque⁽¹¹⁾.

In 1994, H. pylori infection was reported to be one of the infections associated with CHD⁽⁸⁾. By 1998, more than 25 epidemiological studies had reported on the association between H. pylori seropositivity and vascular diseases⁽¹²⁾. Since then, a number of studies have been published with controversial results. Some studies reported weak positive association^(13,14,15,16,17,18,19,20,21), whereas others reported strong association^(8,22,23,24,25,26,27,28,29). Studies performed this far show a high degree of heterogeneity in the selection of patients and also in the type of disease studied, i.e., CHD in general or acute myocardial infarction. Since the pathogenic development is most likely to be different for each of these two conditions (one is chronic and the other is acute), they should be studied separately.

H.pylori infection can cause platelet aggregation and induces a pro-coagulant activity. H.pylori can also contribute to atherosclerosis, through increasing concentration of homocysteine in the blood caused by reduced level of folic acid and cobalamine, or to an autoimmune process⁽⁸⁾.

Fibrinogen which is an important risk factor for ischemic heart disease is shown to be elevated in patients infected with H. pylori⁽³⁰⁾. Virulent CagA-bearing H.pylori strains may contribute to the pathogenesis of early atherosclerosis by aggravating immune-inflammatory reactions⁽³¹⁾.

Methods:

Randomly selected 94 patients admitted with AMI to the intensive care unit of Al-Kindy Teaching Hospital were enrolled in this study. The diagnosis of AMI was made depending on clinical presentation, electrocardiographic changes and plasma biochemical markers (creatin kinase and aspartate aminotransferase). Age and sex matched 94 apparently healthy individuals were taken as a control. A questionnaire stressing possible risk factors was filled including personal habits as smoking, or history of diabetes and hypertension. Body mass index was measured. The following parameters were considered as risk factors for CHD: **Smoking** of 10 or more cigarettes per day

Hypertension if the patient was on anti-hypertensive therapy or has a systolic blood pressure equals or more than 140 mm Hg or a diastolic pressure of 90 mm Hg or more⁽³²⁾.

Diabetes mellitus if the patient was on current dietary modification, on oral hypoglycemic drugs, using insulin or has fasting plasma glucose ≥ 126 mg/dl or random plasma glucose ≥ 200 mg/dl⁽³³⁾.

Lipid profile including cholesterol, LDL, HDL and triglycerides were measured using commercially available kits (bioMerieux). Cholesterol was determined by enzymatic method.

In kits for the determination of High density lipoproteins, the chylomicrons and lipoproteins of very low density (VLDL) and low density (LDL) contained in the sample are precipitated by the addition of phosphotungstic acid in the presence of magnesium ions. The supernatant obtained after centrifugation contains high density lipoproteins (HDL) fraction. This was followed by the determination of cholesterol bound to these fractions.

Determination of LDL is done by the addition of certain amphipathic polymers which precipitate certain lipoprotein fractions specifically. This was followed by the determination of cholesterol and phospholipids bound to these fractions.

Triglycerides were determined using enzymatic methods.

Normal fasting serum lipid profile is considered according to the National Institutes of Health's National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) guidelines⁽³⁴⁾: total cholesterol < 200mg/dl, LDL-cholesterol < 100mg/dl, HDL-cholesterol > 40mg/dl and triglycerides < 150mg/dl

Tests for detection of H.pylori seropositivity: Fasting blood samples were aspirated. Serum was separated as soon as possible after centrifugation of blood, divided into small aliquots and stored at -20C until used. Tests done were Enzyme-linked immuno-sorbent assay (ELISA) for the detection of anti-Helicobacter pylori antibodies using the manufacture's pre-specific cut off value for seropositivity. This

kit is for the detection of IgG class antibodies to H. pylori in serum. It is based on sandwich enzyme immunoassay technique with purified H. pylori bacterial antigen adsorbed on a microwell plate (BioHit, Finland). Statistical analysis was done in both groups using chi square and P-value.

Results:

Table 1 shows the characteristics of traditional risk factors of cases with MI and of age and sex matched controls. Risk factors differ significantly between cases and control. Table 2 shows seropositivity of anti-H. Pylori antibodies in patients with AMI and age and sex matched control. Overall prevalence of anti-H. pylori antibodies in patients with AMI was 82.9% whereas the prevalence in the control group was 78.7% . This difference yielded an odd ratio of 1.317. Chi square test shows that this difference was insignificant statistically (p value 0.458).

Table 1 – characteristics of cases with AMI and of age and sex matched controls

Risk factors	Patient N = 94	Control N = 94	P-value
Age (years)	58.1(11.8)	58.1(11.8)	matched
Sex Male	64(68)	64(68)	matched
Female	30(32)	30(32)	matched
BMI Kg/m ²	29.03(4.8)	26(3.7)	< 0.001
Height(m)	1.68(0.1)	1.7(0.09)	< 0.05
Weight(Kg)	81.8(15.4)	75.2(13.1)	< 0.001
Smokers	48(51)	26(27.6)	0.001
Diabetes	24(25.5)	6(6.3)	< 0.001
Hypertension	38(40.4)	9(9.5)	< 0.001
Total cholesterol (mg/dl)	280(46)	214(38.4)	< 0.001
LDL/C (mg/dl)	172(32)	125(29.5)	< 0.001
HDL/C (mg/dl)	32(3.1)	41.5(4.3)	< 0.001
Triglycerides (mg/dl)			
Male	172(12)	105(10)	< 0.001
Female	145(9)	78(7)	< 0.001

Table 2 - Seropositivity of anti-H. pylori antibodies in patients with AMI and age and

sex matched control			
H.pylori Seropositivity	Patient N = 94 78(82.9%)	Control N = 94 74(78.7)	P – value 0.458

Discussion:

There is contradicting results about the association between H. pylori infection and CHD. In this study we could not prove any association between H. pylori infection and AMI. This contradicting results among the above mentioned different studies (including our study) could be due to many factors:-

1. Possibly the high prevalence of anti-H. pylori antibodies among our population made a significant difference between patients with CHD and normal population difficult⁽¹⁵⁾.
2. The large number of confounding factors may account for the heterogeneity of results and impede clear demonstration of any association. This could be applicable to the contradicting results seen in different studies on the association of H. pylori infection and CHD.
3. The association between H. pylori infection and IHD could be merely a consequence of the strong correlation of H.pylori infection with age and low socioeconomic class.
4. It is well known that the presence of CagA protein in H.pylori is associated with more severe inflammatory response. Particular infection with virulent strains producing the cytotoxin-associated protein CagA may increase the risk of CHD by generation of a persistent low grade inflammatory response⁽³¹⁾. Comparison between the results of such virulent Cag+ and Cag- strain is worth studying. New generation ELISA systems to detect antibodies to These immunogenic proteins are feasible with commercially available kits.

Molecular techniques to detect these genes are more sophisticated process.

5. Measurement of seropositivity in our study was done using the manufacturer's cut off value. It is well known fact that the prevalence of a particular disease has a profound effect in the calculation of the cut off value. The higher the prevalence of the tested disease the more the cut off value. Our kits were manufactured in Finland were the prevalence of H. pylori infection is .much lower than our country. Recalculation of the cut off value by doing the test on a reasonable number of healthy populations is recommended.
6. The small sample size made the interpretation of statistical analysis more difficult. Increasing the sample size will enable more accurate interpretation of results and better adjustment for the several potential confounding factors.
7. Several factors have been identified as being capable of influencing the performance of H pylori serological tests: these include the patients' age, histological findings, H pylori antigens, and, NSAID intake. H.pylori infection and seropositivity have been shown to increase with age. Patients with certain histological abnormalities may be seropositive for H.pylori despite the failure to identify the organism in their gastric biopsy specimens. This is particularly true for cases of chemical gastritis (due to non-steroidal anti-inflammatory drugs) and in patients with chronic atrophic gastritis, thus giving a possibility for many false positive serological tests ⁽³⁵⁾.
8. Qualitative and not quantitative measurement of IgG to H.pylori could have

participated in the discrepancy of results between previous studies⁽³⁶⁾.

9. Current infection with HP is associated with an atherogenic, modified lipid profile. These lipid alterations could explain, at least in part, the reported weak association between chronic HP infection and atherosclerotic diseases⁽³⁷⁾.

In general, although our study, as did many other previous studies, do not support the hypothesis that chronic infection with H.pylori is a major risk factor for AMI, we feel that this issue should be re-evaluated with more detailed and comprehensive approach taking into consideration the following points:-

1. The study should involve large number of patients.
2. The prevalence of H.pylori in the society from which the patient sample is taken should be considered.
3. The study should involve specific age group (young, middle or old) as the prevalence of H.pylori infection is different among different age groups^(25, 35).
4. Since patients may remain seropositive for H.pylori for a long period after successful eradication of the infection with antibiotics (up to 12 months), this seropositivity should be confirmed by other more specific tests such as ¹³C urea breath test or histopathological tests.
5. Concomitant use of other drugs such as non-steroidal anti-inflammatory drugs can affect the specificity of some serological tests⁽³⁵⁾.
6. Serological tests should include quantitative and not merely qualitative measurement of IgG to H.pylori.
7. The strain of H.pylori bacteria should be specified in the serology of future studies because virulent CagA-bearing H.pylori is associated with more severe immune-inflammatory reactions.

References

1. Elliott M. Antman, Eugene Braunwald: Chapter 239; ST-Segment Elevation Myocardial Infarction. In: Fauci, Braunwald, Kasper, Hauser, Longo, Jameson, Loscalzo; **Harrison's Principles of Internal Medicine 17th Ed.**: The McGraw-Hill Companies; **2008**
2. Jeffrey L. Anderson: Chapter 72 ; ST Segment Elevation Acute Myocardial infarction and complications of myocardial infarction. In: Lee Goldman, Dennis Ausiello; **Cecil Medicine, 23rd ed.**: by Saunders, an imprint of Elsevier Inc.; **2008**
3. David D. Waters: Chapter 71; Acute Coronary Syndrome: Unstable Angina and Non-ST Segment Elevation Myocardial Infarction. In: Lee Goldman, Dennis Ausiello; **Cecil Medicine, 23rd ed.**: by Saunders, an imprint of Elsevier Inc.; **2008**
4. Ignatius W. Fong: Emerging relations between infectious diseases and coronary artery disease and atherosclerosis: **CMAJ** • July 11, **2000**; 163 (1)
5. Bora Farsak, Aylin Yildirim, Yakut Akyön, Ahmet Pinar et al: Detection of *Chlamydia pneumoniae* and *Helicobacter pylori* DNA in Human Atherosclerotic Plaques by PCR: **Journal of Clinical Microbiology**, December **2000**, p. 4408-4411, Vol. 38, No. 12
6. Cook PJ and Lip GY. : Infectious agents and atherosclerotic vascular disease. **QJM**; **1996**; 89: 727-35.
7. Folsom AR, Nieto FJ, Sorlie P, Chambless LE, et al: Helicobacter pylori seropositivity and coronary heart disease incidence. Atherosclerosis Risk In Communities (ARIC) Study Investigators. **Circulation**; **1998**; 98: 845-50
8. Pellicano R, Parravicini PP, Bigi R, La-Rovere MT, et al : Patients with acute myocardial infarction in northern Italy are often infected by Helicobacter pylori. **Panminerva-Med**; **1999**; 41: 279-82.
9. HC Jha, J Prasad, and A Mittal: High immunoglobulin A seropositivity for combined Chlamydia pneumoniae, Helicobacter pylori infection, and high-sensitivity C-reactive protein in coronary artery disease patients in India can serve as

- atherosclerotic marker.: **Heart Vessels**, November 1, **2008**; 23(6): 390-6.
10. M Berrutti, R Pellicano, S Fagoonee, M Astegiano, et al: Potential relationship between Helicobacter pylori and ischemic heart disease: any pathogenic model?: **Panminerva Med**, June 1, **2008**; 50(2): 161-3.
 11. Muhlestein JB.: Chronic infection and coronary artery disease. **Med-Clin - North-Am**. **2000**.;84: 123-48
 12. Danesh J, Youngman L, Clark S, Parish S, et al.: Helicobacter pylori infection and early onset myocardial infarction: case-control and sibling pairs study. **BMJ**. **1999**; 319: 1157-62
 13. Brenner H, Berg G, Frohlich M, and Boeing H, et al.: Chronic infection with Helicobacter pylori does not provoke major systemic inflammation in healthy adults: results from a large population-based study. **Atherosclerosis**; **1999**; 147: 399-403
 14. Koenig W, Rothenbacher D, Hoffmeister A, Miller M, et al: Infection with Helicobacter pylori is not a major independent risk factor for stable coronary heart disease: lack of a role of cytotoxin-associated protein A-positive strains and absence of a systemic inflammatory response. **Circulation**: **1999**; 100:2326-31
 15. Reshetnikov OV, Kurilovich SA, Nikitin YuP, Khryanin AA, et al.: Chlamydial but not Helicobacter pylori infection is associated with coronary heart disease in cross-sectional population study (Western Siberian Monica project). XI International workshop on gastroduodenal pathology and H. pylori: **1998**; Abstract 12/353
 16. Murray LJ, Bamford KB, Kee F, McMaster D, et al.: Infection with virulent strains of Helicobacter pylori is not associated with ischaemic heart disease: evidence from a population-based case-control study of myocardial infarction. **Atherosclerosis**: **2000**; 149: 379-85
 17. PM Ridker, J Danesh, L Youngman, R Collins, et al: A Prospective Study of Helicobacter pylori Seropositivity and the Risk for Future Myocardial Infarction among Socioeconomically Similar U.S. Men: **Ann Intern Med**, August 7 , **2001**; 135(3): 184-8
 - 18- A Sotiropoulos, A Gikas, S Skourtis, P Merkouris, et al: Seropositivity to Chlamydia pneumoniae or Helicobacter pylori and coronary artery disease: **Int J Cardiol**, May 24, **2006**; 109(3): 420-1.
 - 19- Zhu J, Quyyumi AA, Muhlestein JB, Nieto FJ, et al: Lack of association of Helicobacter pylori infection with coronary artery disease and frequency of acute myocardial infarction or death: **Am J Cardiol**. **2002** Jan 15;89(2):155-8.
 - 20- AW Haider, PW Wilson, MG Larson, JC Evans, et al: The association of seropositivity to Helicobacter pylori, Chlamydia pneumoniae, and cytomegalovirus with risk of cardiovascular disease: a prospective study: **J. Am. Coll. Cardiol.**, October 16, **2002**; 40(8): 1408-13.
 - 21- Brian E. Lacy and Justin Rosemore: Helicobacter pylori: Ulcers and More: The Beginning of an Era: **Journal of Nutrition**. **2001**;131:2789S-2793S.
 - 22- Gerning NO, Monyyccli P, Axon TR, and Grant PJ,: The association between H. pylori and ischemic heart disease assessed by coronary angiography. **Gut**; **1996**: 39 (Suppl.2): 1C: 10, A91.
 - 23- Caselli M, Kubbajen M, Runa M, Gaudenzi P, et al: Helicobacter pylori and heart. **Gut**; **1996**: 39(Suppl.2): 1C: 17, A92.
 - 24- R Pellicano, MG Mazzarello, S Morelloni, M Ferrari, et al: Helicobacter pylori seropositivity in patients with unstable angina: **J Cardiovasc Surg** (Torino), October 1, **2003**; 44(5): 605-9.
 - 25- Kingo K, Sato H, Shiotani I, Kurotobi T, et al: Prevalence of Helicobacter pylori infection and its link to coronary risk factors in Japanese patients with acute myocardial infarction: **Circ J**. **2002** Sep;66(9):805-10.
 - 26- Kowalski M, Konturek P C, Pieniazek P, Karczewska E, et al: Prevalence of Helicobacter pylori infection in coronary artery disease and effect of its eradication on coronary lumen reduction after percutaneous coronary angioplasty: **Digestive & Liver Disease**; **2001**: 33(3); 222-229.
 - 27- G Di Bonaventura, R Piccolomini, A Pompilio, R Zappacosta, et al: Serum and mucosal cytokine profiles in patients with active Helicobacter pylori and ischemic heart disease: is there a relationship?: **Int J**

Immunopathol Pharmacol, January 1, 2007; 20(1): 163-72.

28- Shereen Attia, Ihab Hamdy, Nasrat Ayad,

Nabeeh El Fadaly: Cytotoxin- Associated Gene – A - Positive Helicobacter Pylori Strains: Risk

Factor for Ischemic Stroke and Coronary Heart Disease: **Heart Views**; March - May 2006: Volume 7 No.1

29- M Miyazaki, A Babazono, K Kadowaki, M Kato, et al: Is Helicobacter pylori infection a risk factor for acute coronary syndromes?: **J Infect**, February 1, 2006; 52(2): 86-91.

30- SW Yusuf and RM Mishra: Effect of Helicobacter pylori infection on fibrinogen level in elderly patients with ischaemic heart disease: **Acta Cardiol**, October 1, 2002; 57(5): 317-22.

31- Manuel Mayr, Stefan Kiechl, Michael A. Mendall, Johann Willeit, et al: Increased Risk of Atherosclerosis Is Confined to CagA-Positive *Helicobacter pylori* Strains: **Stroke**. 2003; 34:610.

32- Theodor A. Kotchen: Chapter 241; Hypertensive Vascular Disease. In: Fauci, Braunwald, Kasper, Hauser, Longo, Jameson, Loscalzo; **Harrison's Principles**

of Internal Medicine 17th Ed.: The McGraw-Hill Companies; 2008.

33- Frier BM, Fisher M.: Diabetes mellitus. In: Nicholas A. Boom, Nicki R. Colledge, Brian R. Walker: **Davidson principles and practice of medicine**. 20thed. Churchill livingstone. 2006: 817-819.

34- Robert S. Porter, Justin L. Kaplan, Barbara P. Homeier, Mark H. Beers: The National Institutes of Health's National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) guidelines: **Merck Manual of Diagnosis and Therapy**, 18thedition;2006

35- Taha AS, Reid J, Boothmann P, Gemmell CG, et al : Serological diagnosis of Helicobacter pylori: Evaluation of four tests in the presence or absence of non-steroidal anti-inflammatory drugs. **Gut**; 1993: 34: 461-5.

36- AM Alkout, EJ Ramsay, DA Mackenzie, DM Weir, et al: Quantitative assessment of IgG antibodies to Helicobacter pylori and outcome of ischaemic heart disease: **FEMS Immunol Med Microbiol**, December 1, 2000; 29(4): 271-4.

37- Albrecht Hoffmeister, Dietrich Rothenbacher, Guenter Bode, Kenneth Persson, et al: Current Infection With Helicobacter pylori, but Not Seropositivity to Chlamydia pneumoniae or Cytomegalovirus, Is Associated With an Atherogenic, Modified Lipid Profile: **Arteriosclerosis, Thrombosis, and Vascular Biology**. 2001; 21:427.

Al – Kindy Col Med J 2011; Vol. 7 No. 2 P: 15

**From the Department of Iraqi Medical Collage /Baghdad University*

Correspondence Address to :Dr. Wathiq K. Abdul-Gafour

Received at : 5th Oct 2009 Accepted at : 4th Jan 2010