Evidence of Infection with Helicobacter Pylori in Patients With Acute Myocardial Infarction

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الدلا ل على الإصابة بالا لكوباكتر با لموري عند مرضى إحتشاء العضلة القلبا ة الحاد

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الخلاصـة

تمهيد: إن دور الإصابة بالا لكوباكتر با لموري كعامل خطورة للإصابة بإحتشاء العضلة القلبا ة الحاد aو محل خلاف.

الأaداف: تقا م العلاقة با ن الإصابة بالا لكوباكتر با لموري وبا ن احتشاء العضلة القلبا ة الحاد.
الطا رق: فا ي aذه الدراسا ة ذات مجموعا ة الضا بط حُا ددت الموجبا ة المصلا ة للغلوبا ولا ين المناعي جا ي المضا اد للا لكوباكتر با لموري عند ٤٠ مرا ضاً مصاباً باحتشاء العضلة القلبا ة الحاد وعند ٣٩ شخصاً من مجموعة الضبط.
النتائج: لم تكن النتائج معتبرة إحصائاً في عموم الدراسة (٨٠% مقابل ٦٩ر٢% وكانت قا مة p ٠ر٢ وOR ٠ر٥٦ و٩٥% CI (٠ر٢-١ر٥))، ولكنا ا كانا ت معتبا رة عنا د الأشا خاص دون سا ن الـ ٥٠ سا نة (١٠٠% مقابل ٦٦ر٧% وقا مة p :٠ر٠٤ وOR ٣ر٢ و٩٥% CI (١ر٤-٠ر٤)). ولم تظا ر aناك علاقة با ن الموجبا ة المصلا ة للا لكوباكتر با لموري وبا ن احتداد عوامل الخطورة الكلاسا كا ة لأمراض الشرا ن التاجا ة.
الإستنتاجات: إنّ aذه الدراسة تبّا ن أنّ الإصابة بالا لكوباكتر با لموري aو عامل خطورة لأمراض الشرا ن التاجا ة في المجموعة العمرا ة التي aي دون الـ ٥٠ سنة.

Abstract

Background: the role of infection with Helicobacter pylori (H. pylori) as a risk factor for acute myocardial infarction is controversial.
Aim of the study: to assess the association between H. pylori infection and acute myocardial infarction.
Patients and Methods: the IgG seropositivity to H. pylori was assessed in 40 patients with acute myocardial infarction and 39 controls.
Results: in the total study the association was statistically insignificant (80% vs 69.2%, p value:0.2, OR 0.56, 95%CI(0.2-1.5)), but in those below the age of 50 years was significant (100% vs 66.7%, p value: 0.04, OR 2.3, 95%CI(1.4-4.02)). No association was found between H. pylori seropositivity and worsening of the classic coronary risk factors.
Conclusion: this study suggests that H. pylori infection is a risk factor for coronary artery disease in patients below 50 years.
Keywords:Helicobacter pylori, acute myocardial infarction

Introduction

Ischaemia refers to lack of oxygen due to inadequate perfusion of the myocardium, which causes imbalance between oxygen supply and demand. The most common cause of myocardial ischaemia is obstructive atherosclerotic disease of epicardial coronary arteries.Ischaemic heart disease causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. With urbanization in the developing world, the prevalence of risk factors for ischaemic heart disease is increasing rapidly in these regions. Large increases in ischaemic heart disease throughout the world are projected, and it is likely to become the most common cause of death worldwide by 2020.

Patients with ischaemic heart disease fall into two large groups: patients with stable angina secondary to chronic coronary artery disease and patients with acute coronary syndromes. The latter group, in turn, is composed of patients with acute myocardial infarction with ST-segment elevation on their presenting electrocardiogram and those with unstable angina and non-ST-segment elevation myocardial infarction. ST-segment elevation myocardial infarction generally occurs when coronary blood flow decreases abruptly after thrombotic occlusion of a coronary artery previously affected by atherosclerosis. Slowly developing, high-grade coronary artery stenoses do not usually precipitate ST-segment elevation myocardial infarction because of the development of a rich collateral network over time. Instead, ST-segment elevation myocardial infarction occurs when a coronary artery thrombus develops rapidly at a site of vascular injury. This injury is produced or facilitated by factors such as cigarette smoking, hypertension, and lipid accumulation. In most cases, infarction occurs when an atherosclerotic plaque fissures, ruptures, or ulcerates and when conditions (local or systemic) favor thrombogenesis so that a mural thrombus forms at the site of rupture and leads to coronary artery occlusion [(1)].

H. pylori was found by Marshal and Warren[(2)] in 1984, and then the bacterium was detected in the gastric mucosa. Numerous studies have reported the association of the bacteria with peptic ulcer, gastric mucosal diseases and gastric cancer. It was reported soon after the discovery of H. pylori that the bacteria are frequently encountered not only in patients with gastropathy but also in healthy individuals. This was because endoscopic examination had been limited to symptomatic patients, and examination in healthy individuals had been difficult. However, since the measurement of serum antibody titers became available, the infection rate in asymptomatic individuals has been indicated to be relatively high. It has also been shown that the infection rate is high (60-80%) in developing countries with poor sanitary conditions and low (30-40%) in advanced western countries, in that age, race, eating habits and geographical and socioeconomic conditions have great influences on the infection rate[(3)].In Iraq its prevalence had ranged between 42.9% and 67% depending on the method that were used[(4)]. The main route of infection transmission is human to human.

Although several classic risk factors for the development of coronary artery disease have been identified (ie hypertension, hypercholesterolaemia, cigarette smoking, diabetes mellitus, and marked obesity), they only explain half of all patients with coronary artery disease (CAD)[(5)].In an effort to better identify patients with CAD, several markers of risk, including infectious agents, have been proposed for screening programs. H. pylori infection has been associated with a higher risk to develop ischaemic heart disease[(6-8)], although the results are controversial[(4,9-11)]. The elucidation of the nature of the relation between this infection and ischaemic heart disease is of major public importance for the prevalence of the infection and the possibility to treat it by antibiotics and acid suppressive drugs.

The role of infection in the pathogenesis of atherosclerosis is still a matter of debate and the underlying processes responsible for any association also remain unclear, but it may be mediated through direct effects of H. pylori on the arterial wall, including smooth muscle cell proliferation, lipid accumulation, endothelial dysfunction, and local inflammation[12], or indirect effects mediated in the circulation through chronic inflammation[13],cross- reactive antibodies[14],or alterations in the classic coronary risk factors(ie diabetes mellitus[15], hypertension[16,17], body mass index[18], and lipid metabolism[19-21]).However, correlations between H. pylori infection and coronary risk factors remain controversial[22].

In this study, patients with acute myocardial infarction were studied and compared with control group for H. pylori seropositivity. Because the association of coronary risk factors with CAD tends to be stronger in younger individuals than in older individuals [23,24], subgroup analysis was performed based on age. Furthermore, the association between H. pylori infection and changes in the classic coronary risk factors was studied.

Aim of the study

To assess the association between helicobacter pylori infection and acute myocardial infarction.

Patients and Methods

Patient and control Subjects

Patients included in this study were 40, had been taken from those who admitted to the coronary care unit in Mirjan teaching hospital with acute ST-segment elevation myocardial infarction between December 2006 and May 2007. A 12 leads ECG was done for each patient and diagnosis of acute myocardial infarction depends on the history of ischaemic chest complaint and ECG changes (ST-segment elevation followed by abnormally persistent Q-wave) as cardiac enzymes were unavailable at the time of the study.

Control subjects were 39 volunteers, had no history of coronary artery disease, and matching patients for age, sex and presence of coronary risk factors (diabetes mellitus, hypertension, smoking and family history).Patients and controls subjects with history of peptic ulcer and chronic dyspepsia had been excluded from the study.

Laboratory Methods

Patients and controls provided venous blood samples that were centrifuged and the serum tested for the presence of IgG antibody by direct agglutination test (by using ACON® Laboratories, Inc. San Diego, CA 92121, USA) which has a sensitivity of 99% and specificity of 86.7% when compared with biopsy/ELISA according to the manufacturer. Measurements of total serum cholesterol, high-density lipoprotein cholesterol and triglycerides concentrations were performed in the hospital laboratory.

Coronary risk factors

Estimation of body mass index (BMI) was done by self measurement of weight and height (BMI=weight kg/height m^2), patients and controls were considered to have diabetes mellitus if they had a history of diabetes mellitus on treatment or fasting blood glucose ≥ 7 mmol/l and hypertension if they had a history of hypertension on treatment, or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, smoking was defined as current or ex-smoker, and patients and controls were asked about the presence of family history of coronary artery disease.

Statistical analysis

All data were coded and tabulated and entered to the computer using statistical package for social sciences (SPSS14), difference between variables measured by using t-test and association between variables measured by using Chi-square test. P value < 0.05 considered as a level of significance.

Results

32 (80%) out of 40 patients with acute myocardial infarction appeared to have positive results to H. pylori, while 27 (69.2%) out of 39 control subjects had positive results to H. pylori, which was not significant (p value: 0.2, OR 0.56, 95%CI(0.2-1.5)). In those below the age of 50 years, all patients, their number was 11 (100%), had positive results to H. pylori, while 8 (66.7%) out of 12 control subjects had positive results to H. pylori, which was significant (p value=0.04, OR 2.3, 95%CI(1.4-4.02)), while in those of 50 years and more , 21 (72.4%) out of 29 patients had positive results to H. pylori and 19 (70.4%) out of 27 control subjects had positive results to H. pylori which was not significant (p value=0.55, OR 0.9,95%CI(0.28-2.88)), (Table 1).

Characteristics of the study population

Table 2 shows the characteristics of patients and controls as a total and those below 50 years, it shows no significant difference between patients and controls except in triglyceride in the total study population and total serum cholesterol for those below 50 years.

Table 1 Incidence of seropositivity to H. pylori IgG antibody in patients and controls subgroups according to age

	Seropositivity to IgG antibody		p value	OR (95%CI)
	Patients n(%)	Controls n(%)		
All	32(80%)	27(69.2%)	0.2	0.56(0.2-1.5)
Age<50 years	11(100%)	8(66.7%)	0.04	2.37(1.40-4.02)
Age≥50 years	21(72.4%)	19(70.4%)	0.55	0.90(0.28-2.88)

Table 2 Characteristics of patients and controls

	Control	Patients	P value	
All				
Age (mean ±SD)	57±12	56.3±10.1	0.47	
Male n(%)				
33(82.5)	30(76.9) }	0.36		
Female n(%)	7(17.5)	9(23.1)		
Diabetes mellitus n(%)	9(22.5)	7(17.9)	0.41	
Hypertension n(%)	7(17.5)	5(12.8)	0.39	
Smoking n(%)				
Not	18(45)	23(59)		
Ex	2(5)	5(12.8) }	0.106	
Current	20(50)	11(28.8)		
Family history n(%)	3(7.5)	3(7.9)	0.63	
Body mass index (mean±SD)	25.4(4)	25.7(3.7)	0.6	
Total cholesterol mmol/l (mean±SD)	4.7±1.2	4.7±1.6	0.97	
HDL cholesterol mmol/l (mean±SD)	1.2±0.4	1.2±0.6	0.79	
Triglyceride mmol/l (mean±SD)	1.6±0.5	2.5±2.2	0.02	.<50 years
Age (mean ±SD)	41.9(5.7)	44.3(2.7)	0.47	
Male n(%)	10(90.9)	11(91.7) }	0.73	
Female n(%)	1(9.1)	1(8.3)		
Diabetes mellitus n(%)	2(18.2)	0	0.21	
Hypertension n(%)	2(18.2)	0	0.21	
Smoking n(%)				
Not	6(54.5)	8(66.7)		
Ex	0	1(8.3) }	0.41	
Current	5(45.5)	3(25)		
Family history n(%)	0	1(8.3)	ND	
Body mass index (mean±SD)	27±4.7	26.2±3.4	0.62	
Total cholesterol mmol/l (mean±SD)	5.6±1.5	3.7±0.6	0.001	
HDL cholesterol mmol/l (mean±SD)	1.2±0.3	1.0±0.4	0.38	
Triglyceridemmol/l (mean±SD)	1.7±0.4	2.2±1.2	0.17	

Comparison of demographic and classic coronary risk factors by H. pylori seropositivity in patients and control There was no significant association between H. pylori seropositivity and any of the coronary risk factors in both patients and controls groups (Table 3). Table 3 Comparison of demographic and classic coronary risk factors in patients and controls by H. pylori seropositivity in the total study.

	Patients		p value	Control		p value
	Positive	Negative		Positive	Negative	
Age (mean±SD)	55.8(12.8)	61.5(6.3)	0.24	56.4(10.1)	56.1(10.1)	0.9
Male (%)	87.5	62.5	0.12	77.8	75	0.57
Diabetes mellitus (%)	21.9	25	0.59	11.1	33.3	0.11
Hypertension (%)	15.6	25	0.43	14.8	8.3	0.5
Smoking (%)						

Not	40.6	62.5		59.3	58.3	
Ex	6.3	_	} 0.47	11.1	16.7	} 0.87
Current	53.1	37.5		29.6	25	
Family history (%)	9.4	_	0.5	7.4	9.1	0.65
BMI (mean±SD)	25.7(4.1)	24.2(3.4)	0.35	26(3.6)	25.2(4.2)	0.59
T.S.Ch.mmol/L(mean±SD)	4.7(1.3)	4.7(1.2)	0.87	5.0(1.8)	4.0(0.8)	0.08
HDL Ch. mmol/L(mean±SD)	1.19(0.4)	1.4(0.3)	0.16	1.3(0.6)	1.09(0.4)	0.17
TG. mmol/L(mean±SD)	1.6(0.5)	1.3(0.4)	0.27	2.7(2.6)	1.9(0.7)	0.3

BMI: body mass index, T.S.Ch.: total serum cholesterol, HDL Ch.: high density lipoprotein cholesterol, TG.: triglyceride

Discussion

Previous studies have shown an association between previous infection with Chlamydia pneumoniae[25,26] or H. pylori[5-7] and the presence of CAD or the risk for an acute coronary event. However, the underlying processes responsible for an association between infectious agents and atherosclerotic diseases remain unclear. Various potential mechanisms, as mentioned, had been proposed, including alteration in classic coronary risk factors, so examination of the association between H. pylori infection and changes in the classic coronary risk factors was done and there were no detrimental effect of H. pylori infection on the classic coronary risk factors, which was consistent with a meta-analysis of 18 studies that involved 10,000 people and which also did not find a strong correlation between H. pylori seropositivity and coronary risk factors[22].

A causal role for H. pylori infection in the pathogenesis of acute myocardial infarction could not be confirmed in this study. In subjects aged <50 years, IgG seropositivity to H. pylori was significantly associated with the onset of acute myocardial infarction. Therefore, direct and/or indirect effects may be important causative factors. First, it has been suggested that chronic direct infection of arteries with H. pylori contributes to the development of atherosclerosis[27,28]. H. pylori has been detected not only in gastric mucosa but also in human atherosclerotic plaques[27,28] and the expression of intercellular adhesion molecule-1 is higher in plaques containing H. pylori than in those which do not[28]. Therefore, local vessel inflammation caused by the presence of H. pylori in plaques may be associated with the development of atherosclerosis. Second, it has been suggested that H. pylori increases the risk of myocardial infarction through the promotion of an enhanced systemic inflammatory response. H. pylori seropositivity is associated with increased concentrations of systemic markers of inflammation (ie fibrinogen, C-reactive protein) and inflammatory cytokines (ie IL-6 and tumor necrosis factor)[29-31]. Systemic markers of inflammation are associated with the onset of myocardial infarction and inflammatory cytokines are believed to activate or injure vascular smooth muscle cells and endothelial cells[32]. Therefore, systemic inflammation from H. pylori infection may be associated with the development of atherosclerosis.

This study had several limitations common to case-control studies. In particular, the possibility that unrecognized population stratification of relevant factors influenced the findings cannot be excluded, specifically the socioeconomic status which is known to affect both the prevalence of H. pylori infection and the risk of CAD[33].

Because the present study examined IgG seropositivity to H. pylori, which can reflect a previous infection, as urea breath test is not available, IgG seropositivity to H. pylori may not reflect an active infection.
Another limitation is that this study does not provide information about the mechanism by which H. pylori plays a role in CAD, so the association of IgG seropositivity to H. pylori and the risk of acute myocardial infarction needs to be confirmed in further prospective studies, and in antibiotic treatment studies for H. pylori eradication, especially in younger individuals.

Conclusion and recommendations

1-this study showed that IgG seropositivity to H. pylori is significantly associated with acute myocardial infarction in patients below the age of 50 years.
2-there were no significant association between H. pylori seropositivity and classical coronary risk factors.
3-these findings can be of particular relevance to direct specific interventions for primary prevention of the disease.
4-given the intrinsic limitations of case-control studies and the relatively small size of the study for interaction analysis, larger prospective studies with the use of antibiotics are necessary to confirm and extend these results

References

1-Dennis L. Kasper, A. S. Fauci, D. L. Longo, E. Braunwald. Harrison's principles of internal medicine, 16th edition, 2005:1436, 1444, 1449.
2-Marshal BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984;I:1311-4.
3-Katsuko H, Yutaka M, Hiroshi K, Toshiji I, Hakuo T. Evidence for infection with H. pylori in patients with acute myocardial infarction. Clinica Chimica Acta 2001;313:87-94.
4-Mushtaq T. Alhassnawi. Helicobacter pylori seropositivity and acute myocardial infartion. FICMS thesis; Baghdad 2005.
5- Braunwald E.Shattuck Lecture:Cardiovascular medicine at the turn of the millennium: Triumphs,concerns,and opportunities. N Engl J Med 1997; 337: 1360-1369.
6- Francesco Z, Augusto D, Andria D, Riccardo N, Domenico D, Maria B, et al. Helicobacter pylori infection and the risk of myocardial infarction Thromb Haemost 1999;82:14-8.
7- R. Pellicano , M.G. Mazzarello, S. Morelloni, M. Allegri , V. Arena.
M. Ferrari, M. Rizzetto .Acute myocardial infarction and Helicobacter pylori . Int J Clin Lab Res (1999) 29:141–144.
8- Danesh J,Youngman L, Clark S, Parish S, Peto R, Collins R. Helicobacter pylori infection and early onset myocardial infarction: Case_control and sibling pairs study. BMJ 1999; 319: 1157-1162.
9- Strachan DP, Mendall MA, Carrington D, Butland BK, Yarnell JW, Sweetnam PM, et al. Relation of Helicobacter pylori infection to 13- year mortality and incident ischemic heart disease in the Caerphilly prospective heart disease study. Circulation 1998; 98: 1286-1290.
10- Barrie R, Daniel M, Jonathan S, John R, Nilesh J. Helicobacter pylori seropositivity in subjects with acute myocardial infarction. Heart 1996;76:308-311.
11- Ridker PM, Danesh J,Youngman L,Collins R, Stampfer MJ, Peto R, 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 2001; 135: 184-188.
12- Epstein SE, Zhou YF, Zhu J. Infection and atherosclerosis: Emerging mechanistic paradigms. Circulation 1999; 100: e20-e28.

13- Patel P, Mendall MA, Carrington D, Strachan DP, Leatham E, Molineaux N, et al. Association of Helicobacter pylori and Chlamydia pneumoniae infections with coronary heart disease and cardiovascular risk factors. BMJ 1995; 311: 711-714.
14- Birnie DH, Holme ER, McKay IC, Hood S, McColl KE, Hillis WS. Association between antibodies to heat shock protein 65 and coronary atherosclerosis: Possible mechanism of action of Helicobacterpylori and other bacterial infections in increasing cardiovascular risk. Eur Heart J 1998; 19: 387-394.
15- Marrollo M, Latella G, Melideo D, Storelli E, Iannarelli R, Stornelli P, et al. Increased prevalence of Helicobacter pylori in patients with diabetes mellitus. Dig Liver Dis 2001; 33: 21-29.
16- Lip GH, Wise R, Beevers G. Association of Helicobacter pylori infection with coronary heart disease: Study shows association between H. pylori infection and hypertension. BMJ 1996; 312: 250- 251.
17- Harvey R, Lane A, Murray L, Harvey I, Nair P, Donovan J. Effect of Helicobacter pylori infection on blood pressure: A community based cross sectional study. BMJ 2001; 323: 264-265.
18- Ekesbo R, Nilsson PM, Lindholm LH, Persson K, Wadstrom T. Combined seropositivity for H. pylori and C. pneumoniae is associated with age, obesity and social factors. J Cardiovasc Risk 2000; 7: 191-195.
19- Niemela S, Karttunen T, Korhonen T, Laara E, Karttunen R, Ikaheimo M, et al. Could Helicobacter pylori infection increase the risk of coronary heart disease by modifying serum lipid concentrations? Heart 1996; 75: 573-575
20- Laurila A, Bloigu A, Nayha S, Hassi J, Leinonen M, Saikku P. Association of Helicobacter pylori infection with elevated serum lipids. Atherosclerosis 1999; 142: 207-210.
21- Hoffmeister A, Rothenbacher D, Bode G, Persson K, Marz W, Nauck MA, et al. Current infection with Helicobacter pylori, but not seropositivity to Chlamydia pneumoniae or cytomegalovirus, is associated with an atherogenic, modied lipid profile. Arterioscler Thromb Vasc Biol 2001; 21: 427-432.
22- Danesh J, Peto R. Risk factors for coronary heart disease and infec- tion with Helicobacter pylori: Meta-analysis of 18 studies. BMJ1998; 316: 1130-1132.
23- Prospective Studies Collaboration. Cholesterol, diastolic blood pres- sure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts: Prospective studies collaboration. Lancet 1995; 346: 1647-1653.
24- Parish S, Collins R, Peto R, Youngman L, Barton J, Jayne K, et al. Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14,000 cases and 32,000 controls in the United Kingdom: The International Studies of Infarct Survival (ISIS) Collaborators. BMJ 1995; 311: 471-477.
25- Kosaka C, Hara K, Komiyama Y, Takahashi H. Possible role of chronic infection with Chlamydia pneumoniae in Japanese patients with acute myocardial infarction. Jpn Circ J 2000; 64: 819-824.
26- Song H, Tasaki H, Yashiro A, Yamashita K, Taniguchi H, Nakashima Y. Acute-phase proteins and Chlamydia pneumoniae infection: Which one is more important in acute coronary syndrome? Jpn Circ J 2001; 65: 853-857.

27- Farsak B, Yildirir A, Akyon Y, Pinar A, Oc M, Boke E, et al. Detec- tion of Chlamydia pneumoniae and Helicobacter pylori DNA in human atherosclerotic plaques by PCR. J Clin Microbiol 2000; 38: 4408-4411.
28- Ameriso SF, Fridman EA, Leiguarda RC, Sevlever GE. Detection of Helicobacter pylori in human carotid atherosclerotic plaques. Stroke 2001; 32: 385-391.
29- Patel P, Carrington D, Strachan DP, Leatham E, Goggin P, North_eld TC, et al. Fibrinogen: A link between chronic infection and coronary heart disease. Lancet 1994; 343: 1634-1635.
30- Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C reactive protein and its relation to cardiovascular risk factors: A population based cross sectional study. BMJ 1996; 312: 1061-1065.
31- Crabtree JE, Shallcross TM, Heatley RV, Wyatt JI. Mucosal tumour necrosis factor alpha and interleukin-6 in patients with Helicobacter pylori associated gastritis. Gut 1991; 32: 1473-1477.
32- Libby P, Egan D, Skarlatos S. Roles of infectious agents in athero- sclerosis and restenosis: An assessment of the evidence and need for future research. Circulation 1997; 96: 4095-4103.
33- Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: Is there a link? Lancet 1997; 350: 430-436.