Serum concentrations of *Helicobacter pylori* IgG and the virulence factor CagA in patients with ischaemic heart disease

A. Jafarzadeh,[1] A. Esmaeeli-Nadimi,[2] M. Nemati,[1] M. Tahmasbi[2] and P. Ahmadi[1]

التـراكيز المصلية للغلوبولين المناعي «الأيج–ج» المضاد للمَلْوِيَّات البوَّابية ولعامها الفوعي CagA في المصابين بمرض القلب الإقفاري

عبد الله جعفرزاده، علي إسماعيلي نديمي، مريم نعمتي، مريم طهماسبي، بروديس أحمدي

الخلاصـة: في سبيل مقارنة التـراكيز المصلية للغلوبولين المناعي «الأيج–ج» IgG المضاد للملويّات البوابية وعامها الفَوْعي CagA، بين المصابين بمرض القلب الإقفاري وبين الشواهد؛ قام الباحثون بدراسة 120 مصاباً بمرض القلب الإقفاري، منهم 60 مصاباً باحتشاء عضل القلب الحادّ، و60 مريضاً بالذبحة غير المستقرة في مقابل 60 من الشواهد الأصحاء المتماثلين مع المرضى من حيث العمر والجنس. ووجد الباحثون أن معدَّل الانتشار المصلي للأيج–ج المضاد للملويّة البوابية في المصابين بالاحتشاء الحاد يبلغ 86.7٪، وفي المصابين بالذبحة غير المستقرة 91.7٪، في حين يبلغ في الشواهد الأصحاء 58.3٪، حيث بلغ وسطيُّ عياراته في المصابين بالاحتشاء 33.2 وحدة/ مل (مع خطأ معياري مقداره 4.76)، وفي المصابين بالذبحة غير المستقرة 57.96 وحدة/ مل (مع خطأ معياري مقداره 7.54)؛ في حين بلغ في الشواهد الأصحاء 25.72 وحدة/ مل (مع خطأ معياري مقداره 4.01). وعلى هذا فإن معدّل الانتشار المصلي للغلوبولين المناعي المضاد للملويّة البوابية في مجموعتي المرضى أعلى بنسبة يُعتدُّ بها إحصائياً مما هو عليه لدى مجموعة الشواهد الأصحاء. كما كان وسطي مستوى الأيج–ج المضاد للملويات البوابية لدى مرضى احتشاء عضل القلب والذبحة غير المستقرة أعلى بمقدار يُعْتَدُّ به إحصائياً مما هو عليه لدى مجموعتَيْ الشواهد. كما وجد الباحثون أن معدَّل الانتشار المصلي والعيار الوسطي للأيج–ج المضاد للعامل الفَوْعي CagA لم يختلفا اختلافاً يُعْتَدُّ به إحصائياً بين مجموعَتَيْ المرضى ومجموعة الشواهد.

ABSTRACT To compare the serum concentrations of IgG to *Helicobacter pylori* and its virulence factor CagA in patients with ischaemic heart disease (IHD), we recruited 120 patients with IHD [acute myocardial infarction (AMI) (*n* = 60); unstable angina (UA) (*n* = 60)] and 60 sex- and age-matched healthy controls in this study. The seroprevalence of anti-*H. pylori* IgG was 86.7% in AMI, 91.7% in UA patients and 58.3% in the control group with mean titres of 33.2 U/ml [standard error (SE) 4.76], 57.96 U/ml (SE 7.54) and 25.72 U/ml (SE 4.01) respectively. The seroprevalence of anti-*H. pylori* in the patient groups was significantly higher than the control group. The mean levels of anti-*H. pylori* in the AMI and UA groups were also significantly higher than in the control group. The seroprevalence and mean titre of anti-CagA IgG did not differ significantly between patient and control groups.

Concentrations sériques d'IgG anti-*Helicobacter pylori* et facteur de virulence CagA chez les patients souffrant de cardiopathie ischémique

RÉSUMÉ Afin de comparer les concentrations sériques de l'IgG anti-*Helicobacter pylori* et son facteur de virulence CagA chez les patients souffrant de cardiopathie ischémique (CI), nous avons recruté dans cette étude 120 patients souffrant de ce type d'affection [infarctus aigu du myocarde (IAM) (*n* = 60) ; angine de poitrine instable (API (*n* = 60)] et 60 témoins en bonne santé appariés selon l'âge et le sexe. La séroprévalence de l'IgG anti-*H.pylori* était de 86,7 % chez les patients IAM, 91,7 % chez les patients API et 58,3 % dans le groupe témoin avec des titres moyens de 33,2 U/ml [erreur-type (ET) 4,76], 57,96 U/ml (ET 7,54) et 25,72 U/ml (ET 4,01) respectivement. La séroprévalence de l'IgG anti-*H.pylori* dans les groupes de patients était nettement supérieure à celle du groupe témoin. Les taux moyens d'IgG anti-*H.pylori* dans les groupes IAM et API étaient également nettement supérieurs à ceux du groupe témoin. La séroprévalence et le titre moyen de l'IgG anti-CagA ne présentaient pas de différence significative entre les groupes de patients et le groupe témoin.

[1]Department of Immunology, Medical School; [2]Department of Internal Medicine, Ali-ebne-Abitaleb Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Islamic Republic of Iran (Correspondence to A. Jafarzadeh: Jafarzadeh14@yahoo.com).

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Introduction

A number of etiological factors have been determined for development of ischaemic heart disease (IHD). Although there are several major known risk factors for the development of coronary artery disease, about 50% of patients with this condition do not have any of these risk factors [1]. It has been suggested that inflammatory reactions may play an important role in the pathogenesis of IHD [2] An association between IHD and some infectious agents including *Chlamydia pneumoniae*, herpes simplex virus (HSV), cytomegalovirus (CMV) and hepatitis A, respiratory tract and dental infection has been reported in some epidemiological studies [2]. However, some prospective studies failed to demonstrate a strong relationship between the presence of IgG antibodies to *C. pneumoniae*, HSV-1 and CMV and the occurrence of coronary arterial disease [3]. Some investigators also have assessed the relationship between *H. pylori* and IHD, reporting a strong positive association [4–6] a moderate association [7–10] and even negative association [11–14].

Strains of *H. pylori* are genetically diverse and have been divided into type I and type II according to the expression or non-expression of cytotoxin-associated gene A (CagA) [15]. CagA has been identified as a virulence marker of *H. pylori* and the cagA+ strains induce more severe disease and inflammatory response [15]. Since CagA is immunodominant, the detection of serum IgG to the CagA antigen has been reported as a reliable marker of carriage of cagA+ *H. pylori* strains [16]. We have recently reported that the seroprevalence of *H. pylori* in healthy Iranian adults was 67.5% and in healthy children 46.6%; the prevalence of anti-CagA antibody was 72.8% in infected adults and 67.4% in infected children [17].

Elevated levels of C-reactive protein (CRP), fibrinogen, homocysteine, pro-inflammatory cytokines and antibodies to some heat shock proteins are known to be associated with an increased risk of cardiovascular events [18]. Chronic infections such as *H. pylori* may be behind these changes. However, the role of *H. pylori* as a risk factor for IHD remains debatable. This study was conducted for the first time to evaluate the seroprevalence of antibody to *H. pylori* and bacterial virulence factor CagA in Iranian patients with IHD to clarify the possible relationships.

Methods

A total of 120 patients aged 40–65 years with IHD who were admitted to Ali-Ebne-Abitaleb Hospital in Rafsanjan (a city in Kerman province in the southeast of the country) during the period March–December 2007 were enrolled to this cross-sectional, case-controlled study. Sample size was calculated at 50 (using P1 = 90%; P2 = 60%; α = 5%; β = 10%), which was increased to 60 in each group for the actual sample, i.e. 120 patients altogether. Patients were classified into 2 groups according to well-established criteria as having acute myocardial infarction (AMI) or unstable angina (UA). AMI was diagnosed by the presence of 2 of these criteria: prolonged chest pain compatible with AMI, typical ECG changes, elevation of cardiac enzymes. Patients with non-ST elevation were excluded from the study. UA was defined according to Braunwald's classification and all patients had chest pain at rest with definite ischaemic electrocardiographic changes such as ST-segment changes and/or T-wave inversion; all UA patients were in class IIIB according to Braunwald's classification [3]. Exclusion criteria were valvular heart disease, surgery, trauma within the previous month, cardiomyopathy, liver disease, renal failure, malignant diseases, other inflammatory disease (such as septicaemia and pneumonia) and oral anticoagulant therapy. A third sex- and age-matched group with similar geographic and socioeconomic status comprised 60 subjects without any IHD, registered as a control group. The healthy control group was recruited from blood donors at Rafsanjan Blood Transfusion Centre. All patients and controls were residents of Rafsanjan city.

The study was evaluated and approved by the Ethical Committee of Rafsanjan University of Medical Sciences. Informed consent was given and all those recruited had agreed to give blood samples.

Peripheral blood (2–4 mL) was collected from the participants in the 3 groups and the serum separated and stored at –20 °C. In patients with AMI the serum samples were collected during 3–5 days after admission; in patients with UA they were collected at admission.

Determination of *H. pylori*-specific antibodies in serum

The serum levels of anti-*H. pylori* immunoglobulin G (IgG) were measured using a commercial enzyme-linked immunosorbent assay (ELISA) (Trinity Biotec, Ireland) according to the manufacturer's guidelines. The results were expressed as U/mL and a cut-off value of 5 U/mL was used to discriminate negative from positive samples.

Serum levels of anti-CagA IgG were also assayed by ELISA using commercial kits (Diagnostic Bioprobes, Italy). The serum concentrations of anti-CagA antibodies were expressed in arbitrary units (Uarb/mL) as no international standard is available. According to the manufacturer's guidelines, a cut-off value of 5 Uarb/mL was used to discriminate negative from positive samples. The serum concentrations of anti-*H. pylori* and anti-CagA antibodies were expressed as mean and standard error (SE).

Statistical analysis

Differences in variables were analysed using analysis of variance, *t*-test, Mann–Whitney U test, Kruskal–Wallis test

and Chi-squared test as appropriate, and *P*-values < 0.05 were considered significant. All the available data were analysed using *SPSS*, version 15.0.

Results

Baseline characteristics

Baseline characteristics of the participants are shown in Table 1. The patient and control groups were similar in age and male/female ratio, but patients had significantly higher prevalence of classic risk factors for IHD (hypertension, dyslipidaemia and diabetes) compared with the control group.

Anti-*H. pylori* IgG seropositivity

The overall seroprevalence of anti-*H. pylori* IgG was 89.2% among patients with IHD and 58.3% among healthy controls with mean titre 45.58 U/mL (SE 4.58) and 25.72 U/mL (SE 4.01) respectively. The prevalence of anti-*H. pylori* IgG was significantly higher in IHD patients compared to the control group ($P < 0.0001$). The mean titre of anti-*H. pylori* antibodies in the IHD group was significantly higher than that observed in the control group ($P < 0.01$) (Table 2). The seropositivity rate of anti-*H. pylori* antibody was 86.7% and 91.7% in the AMI and UA groups with mean titre of 33.2 U/mL (SE 4.76) and 57.96 U/mL (SE 7.54) respectively. The seroprevalence of anti-*H. pylori* antibodies in AMI and UA groups was also significantly higher compared to the control group ($P < 0.0001$). The mean titre of anti-*H. pylori* antibodies in AMI and UA groups was significantly higher than that observed in control group ($P < 0.05$ and $P < 0.001$ respectively). The seroprevalence of anti-*H. pylori* was similar in patients with AMI and UA. No significant difference was observed between the AMI and UA groups regarding the mean titre of anti-*H. pylori* antibodies (Table 2).

Anti-CagA seropositivity

The overall seroprevalence of anti-CagA IgG was 60.7%in *H. pylori*-infected patients with IHD and 65.7% in infected asymptomatic healthy subjects; mean titres were 37.68 Uarb/mL (SE 8.35) and 16.84 Uarb/mL (SE 2.88) respectively. There was no significant difference between IHD and control groups regarding the prevalence of anti-CagA antibodies. There was no significant difference between IHD and control groups regarding the mean titre of serum anti-CagA antibodies, although this parameter was higher in the IHD group in comparison to asymptomatic healthy subjects. The seropositivity rate of anti-CagA antibody was 55.8% and 65.5% in *H. pylori*-infected patients with AMI and UA respectively; mean titres were 42 Uarb/mL (SE 15.42) and 33.61 Uarb/mL (SE 7.32) respectively (Table 2).

Statistical analysis showed that the differences for both seroprevalence and mean titre of anti-CagA antibodies were not significant between the AMI and UA groups compared to the control group. The prevalence and the mean titre for anti-CagA antibodies were similarly expressed in patients with AMI and UA (Table 2).

Discussion

In this study the seroprevalence of anti-*H. pylori* IgG and the mean titre of anti-*H. pylori* antibodies were significantly higher in patients with IHD compared to the healthy control group. The seropositivity rate for *H. pylori* infection varies greatly between studies (Table 3). Moreover, the association of *H. pylori* with IHD may also differ between countries or even within a country. The discrepancies may be attributed largely to differences in age, socioeconomic status, race and ethnic background. Moreover, different inclusion criteria of patients and controls used in the various studies, differences in the distribution of traditional risk factors of IHD and genetic heterogeneities of *H. pylori* may account for some differences. Accordingly, the results of one study may not necessarily apply to other populations, even within the country.

H. pylori infection might participate in IHD pathogenesis via direct or indirect effects. The presence of *H. pylori* DNA has been demonstrated in the aortic tissues and atherosclerotic plaques of the majority patients with coronary heart disease, which could be an important indication of the direct role of bacteria in the pathogenesis of disease [19]. Accordingly, *H. pylori* can directly provoke inflammation within the atherosclerotic plaques.

Table 1 Baseline characteristics of patient and control groups

Characteristic	Acute myocardial infarction (*n* = 60)	Unstable angina (*n* = 60)	Controls (*n* = 60)	*P*-value[a]
Mean (SEM) age (years)	54.6 (9.7)	55.8 (9.6)	52.98 (8.7)	NS
Sex (men/women) (No.)	39/21	35/25	33/27	NS
Hypertension (No.)	7	8	0	0.01
Dyslipidaemia (No.)	10	6	0	0.01
Diabetes mellitus (No.)	7	9	0	0.01

[a]*Comparing all patients with ischaemic heart disease and healthy control group.*
SEM = standard errof of the mean.

Table 2 Association of *Helicobacter pylori* and CagA in patients with ischaemic heart disease (IHD) compared to the control group

Variable	Control group	IHD group	AMI group	UA group
Seroprevalence of anti-*H. pylori* (%)	58.3	89.2***	86.7***	91.7***
Serum anti-*H. pylori* (U/mL) [Mean (SE)]	25.72 (4.01)	45.58** (4.58)	33.2* (4.76)	57.96*** (7.54)
Serum anti-CagA (Uarb/mL) [Mean (SE)]	16.84 (2.88)	37.68 (8.35)	42 (15.42)	33.61 (7.32)

**P < 0.05; **P < 0,01; ***P < 0.001 compared to control group.*
AMI = acute myocardial infarction.
UA = unstable angina.

Our results showed no significant differences between patient and control groups regarding the prevalence of serum anti-CagA antibodies, which indicates that CagA-positive strains were not more related to IHD in comparison to CagA-negative strains. However, the results of a systematic meta-analysis confirm the hypothesis that infection with CagA-seropositive strains is significantly associated with susceptibility to coronary heart disease [20]. The controversial results of some studies regarding the association of CagA status of *H. pylori* with IHD have been summarized in Table 4. It has also been reported that there is wide geographical variation in the genotype of CagA+ strains [24]. Moreover, the polymorphisms in genes encoding for some cytokines such as IL-1, TNF-α and IFN-γ have been associated with *H. pylori*-related diseases such as gastric cancer and peptic ulcer [25]. Accordingly, it seems that both host and bacterial factors may account for these differences. Further studies on the interaction between *H. pylori* and the host genotype, which in turn could determine the intensity of the inflammatory responses, may explain the development of IHD in some *H. pylori*-infected subjects.

Consistent with our findings in the present study, we recently observed that serum concentrations of hs-CRP were not affected by the expression of bacterial CagA virulence factor [26]. However, in our previous study in the same population, an important association was observed between infection with CagA-positive *H. pylori* strains and peptic ulcer [27], which indicate that the role of the CagA-positive strains may differ in peptic ulcer and IHD pathogenesis.

We have demonstrated that the mean titre of anti-*H. pylori* antibodies in patients with IHD was significantly higher than that observed in a control group. Moreover, the mean serum levels of anti-CagA antibodies were higher in patients than controls, but the differences were not statistically significant. Recently, cross-reactivity between rabbit serum with high levels of anti-*H. pylori* and antigens from atherosclerotic carotid arteries has been demonstrated [28]. It has been also shown that anti-CagA antibodies are capable of reacting with both bacterial CagA and proteins present in the wall of arteries, providing evidence of molecular mimicry between CagA and vascular antigens [29]. Accordingly, it has been suggested that CagA-positive strains of *H. pylori* may contribute to the destabilization of coronary atherosclerotic plaques in some patients with acute coronary syndrome. From these findings, it seems that both anti-*H. pylori* and anti-CagA antibodies may have an important role in the pathogenesis of IHD.

Further prospective studies are needed to assess the relationship between exposure to *H. pylori* and subsequent risk of ischaemic heart disease. Because *H. pylori* infection may be easily eradicated by specific treatments, the accurate definition of this new risk factor may lead to the design of possible novel strategies for the prevention of ischaemic heart disease. Recent studies have highlighted the importance of the

Table 3 Comparison of the association of *Helicobacter pylori* and ischaemic heart disease (IHD) in selected studies

Country	*H. pylori* seropositivity (%)		*P*-value	Reference
	IHD	Controls		
India	98	57	0.001	4
	77	43	0.001	4
	58	53	NS	11
Turkey	60.2	57.7	NS	12
	78.8	58.3	0.05	7
Greece	77	68	NS	13
	55.1	39.6	0.05	8
Italy	78.3	56.2	0.05	9
	84.7	61.8	0.0001	5
	78.7	76.2	NS	14
Japan	58.7	43.3	0.009	6
	87.9	66.7	0.05	10
Islamic Republic of Iran	89.2	58.3	0.0001	Present study

NS = not significant

Table 4 Comparison of the association of anti-CagA seropositivity with ischaemic heart disease (IHD) in selected studies

Country	Anti-CagA seropositivity (%)		*P*-value	Reference
	IHD	Controls		
Italy	33.8	26.8	0.0001	5
	71.4	52.4	0.03	14
Japan	72.7	57.6	0.05	10
Germany	27.9	21.7	NS	21
Poland	81	85	NS	22
United Kingdom	52	43	0.023	23
Islamic Republic of Iran	60.7	65.7	NS	Present study

association the of number of pathogens (pathogen burden) by which an individual has been infected with IHD [30]. Accordingly, the application of broader strategies, not only against *H. pylori* but also against *C. pneumoniae* and other infectious organisms such as those causing chronic bronchitis and periodontitis, may be considered for the prevention of ischaemic heart disease.

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Fact sheet N°317 Cardiovascular diseases (CVDs):
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- CVDs are the number one cause of death globally: more people die annually from CVDs than from any other cause.
- An estimated 17.1 million people died from CVDs in 2004, representing 29%of all global deaths. Of these deaths, an estimated 7.2 million were due to coronary heart disease and 5.7 million were due to stroke.
- Low- and middle-income countries are disproportionally affected: 82% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women.
- By 2030, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke. These are projected to remain the single leading causes of death. The largest percentage increase will occur in the Eastern Mediterranean Region. The largest increase in number of deaths will occur in the South-East Asia Region.