

Assessment of the relationship between serum fibrinogen level and chronic *Helicobacter pylori* infection in patients with or without ischemic heart disease

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Abstract

Background: Infectious agents such as *Chlamydia pneumonia* or *Helicobacter pylori* (*H. pylori*) have been linked to ischemic heart disease (IHD) as the epidemiologic studies have shown. Other studies believed that raised plasma fibrinogen level has been claimed as a possible link between *H. pylori* infection and IHD.

Methods: An analytic cross-sectional study was undertaken on 261 patients. 131 hospitalized patients were selected from CCU ward, as cases and 130 hospitalized patients from surgery and orthopedic wards of Iran University of Medical Sciences hospitals, as controls. HP infection, serum fibrinogen level and cardiovascular risk factors were determined in all cases and controls. T-test, chi-square test, general linear model and logistic regression model were used in analysis.

Results: *H. pylori* infection was not in association with IHD. High fibrinogen level was also not associated with IHD in cases with *H. pylori* infection.

Conclusion: Although there was no link between *H. pylori* infection, fibrinogen level and IHD in this study, some authors believe that the probable mechanism of this association is that under stimulation by the bacterium, mononuclear cells produce a tissue factor-like procoagulant activity that, through the extrinsic pathway of blood coagulation, converts fibrinogen to fibrin.

Keywords: *Helicobacter pylori*, ischemic heart diseases, fibrinogen

Introduction

In the last few years, besides local tissue damage, an association between *Helicobacter pylori* (HP) infection and various extra-intestinal pathologies such as ischemic heart disease, ischemic cerebrovascular disease, atherosclerosis, Raynaud's phenomenon and skin diseases has also been described [1-4]. A large number of studies have reported the associations between human coronary heart disease

(CHD) and certain persistent bacterial infections such as HP and *Chlamydia pneumonia* [5-6]. Meanwhile, some other studies believe that high levels of fibrinogen can be a probable link between HP and ischemic heart disease (IHD) [7-9].

Fibrinogen is an acute phase reactant protein which may only show systemic inflammation and it may not have any relation to the underlying disease [10].

On the other hand, although major risk factors of IHD are known, these factors can not express the pathogenesis of the disease [11].

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More than 20 epidemiologic studies during the past years have shown the relation between HP and IHD and a meta-analysis believes that there is a weak association between these subjects, too [5].

Most of these documents are derived from small case-control studies which either do not take consideration into confounding factors or only match some limited confounders while prospective studies do not suggest an independent relationship [4-15].

In another meta-analysis a strong relation between HP and different markers of systemic inflammation has been shown in some studies [16]. This study believes that this association is due to publication bias (the preference of publication of papers that suggest the presence of the relation in comparison with no relation) by journals. However, some other studies have expressed that markers of systemic inflammation can also potentially be under consideration in pathophysiology of IHD [17].

Our previous study could not show the relation between HP and IHD [18]. That study [18] and a similar one [8] showed that if there is a relation, it is explainable more through association between HP and different known cardiovascular risk factors. Thus, considering the importance of IHD as the first mortality factor in Iran, we decided to evaluate the role of fibrinogen in probable relation between HP and IHD.

In the present study, we selected persons with minimum IHD risk factors and divided them into two groups with (cases) and without (controls) IHD. The impact of other IHD risk factors were minimized so that fibrinogen role could be expressed more clearly.

Methods

This analytic cross-sectional study was performed in educational hospitals of Iran University of Medical Sciences in Tehran, Iran during 2000-2001. By assumption of $\alpha=0.05$, power =80%, frequency of patients with coronary artery disease (CAD) and anti-HP IgG positive

(cases) equal to 77%, frequency of people without CAD but anti-HP IgG positive (controls) was 59% [19] and comparing two ratios formula; sample size was calculated as 130 individuals in each group. Also sampling was performed using non-probability convenience method.

Cases were selected from hospitalized patients in CCU. Type of CAD [myocardial infarction (MI) or unstable angina (UA)] was determined according to history, ECG and cardiac enzyme levels (AST, CPK and LDH). Controls enrolled in the study were from patients hospitalized in surgical and orthopedic wards of the same hospitals, simultaneously. Eligibility criteria consisted of patients with the least risk factor for IHD, age more than 30 years old and no past history of peptic ulcer diseases (PUD) or GI bleeding. In the control group, in addition to these criteria, patients should not have a past history of CAD or cerebrovascular accident (CVA). Age, sex, weight, job, educational level and risk factors of CAD were determined for all samples using a check list.

Moreover, a blood sample was taken for titrating anti-HP IgG and fibrinogen from all patients, using ELISA method. IgG level equal or more than 0.1 was positive in this study. Plasma fibrinogen level was determined according to a clotting method named CLAUSS. In addition, all the samples were evaluated in a single laboratory and by a single technician in order to omit interobserver bias.

SPSS statistical software package, version 11.5 was utilized for statistical analysis. Quantitative variables were analyzed using student's T test. In the case of Qualitative variables, Chi-square test was used. Correlation coefficients such as Phi and Eta, odds ratio (OD) and its 95% confidence interval were used, whenever needed. Univariate General Linear Model for deletion of confounder effect and Wald forward logistic regression analysis for determining IHD risk factors were also used.

A P-value of <0.05 was considered to be statistically significant. In addition, study protocol

| Variable | No. | Frequency (%) |
|---------------------------------------|-----|---------------|
| Sex (<i>male</i>) | 167 | 64 |
| Anti-Helicobacter Pylori IgG positive | 112 | 42.9 |
| Job | | |
| <i>Household</i> | 87 | 33.3 |
| <i>Employer</i> | 36 | 13.8 |
| <i>Free</i> | 131 | 50.2 |
| <i>Without job</i> | 7 | 2.7 |
| Education | | |
| <i>Illiterate</i> | 116 | 44.4 |
| <i>Elementary school</i> | 103 | 39.5 |
| <i>High school</i> | 33 | 12.6 |
| <i>University degree</i> | 9 | 3.4 |

Table 1. Basic characteristics of all the patients.

conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Results

Basic characteristics of the study population are summarized in Table 1. In the case group, there were 109 (83.3%) patients with MI and 22 (16.7%) patients with UA.

Cases were significantly older than controls [54.83 (53.32 - 56.35) vs. 47.68 (45.76 - 49.61)

years; $P < 0.001$, $\text{Eta} = 0.338$]. Moreover, they had significantly more weight, too [68.69 (67.45 - 69.94) vs. 65.53 (64.35 - 66.71) kg; $P < 0.001$, $\text{Eta} = 0.221$].

Also, lower education level ($P = 0.002$), smoking (29% vs. 6.9%, $P < 0.001$) and hypertension (22.1% vs. 12.3%, $P < 0.001$) were significantly more common among cases in comparison with controls.

Sex and job distributions were similar in both

| Variable | Case n=131 | Control n=130 | P-value |
|--|------------------|-------------------|---------|
| Sex (<i>male</i>) % | 85(64.9%) | 82(63.1) | 0.861 |
| Age (<i>year</i>) Mean \pm SD | 54.83 \pm 8.77 | 47.68 \pm 11.07 | <0.001* |
| Weight (<i>Kg</i>) Mean \pm SD | 68.69 \pm 7.20 | 65.53 \pm 6.78 | <0.001* |
| Smoking (<i>positive</i>) % | 38(29%) | 9(6.9%) | <0.001* |
| Hypertension (<i>positive</i>) % | 29(22.1%) | 16(12.3%) | <0.001* |
| Job % | | | |
| <i>Household</i> | 44(33.6%) | 43(33.1%) | 0.627 |
| <i>Employer</i> | 16(12.2%) | 20(15.4%) | |
| <i>Free</i> | 66(50.4%) | 65(50%) | |
| <i>Without job</i> | 5(3.8%) | 2(1.5%) | |
| Education % | | | |
| <i>Illiterate</i> | 70(53.4%) | 46(35.4%) | 0.002* |
| <i>Elementary school</i> | 42(32.1%) | 47(36.2%) | |
| <i>High school</i> | 16(12.3%) | 31(23.8%) | |
| <i>University degree</i> | 3(2.3%) | 6(4.6%) | |
| Anti-helicobacter pylori IgG (<i>positive</i>) % | 74(56.3%) | 57(43.8%) | 0.116 |
| Fibrinogen (<i>positive</i>) % | 13(9.9%) | 13(10%) | 0.984 |

* Significant statistical difference

Table 2. Basic and main characteristics of the study.

| Risk factors | Odds ratio | 95% confidence interval | P-value |
|---------------------|------------|-------------------------|---------|
| <i>Age</i> | 1.06 | 1.04-1.1 | <0.001 |
| <i>Weight</i> | 1.05 | 1.01-1.09 | 0.023 |
| <i>Smoking</i> | 6.37 | 2.75-14.76 | <0.001 |
| <i>Hypertension</i> | 2.28 | 1.11-4.7 | 0.025 |

Table 3. Odd ratios of risk factors for coronary heart disease.

groups. The prevalence of HP infection was 56.3% in cases and 43.8% in controls which was not statistically significant even after deletion of confounding effects of age, weight and CAD risk factors ($P>0.05$). All demographics and main variables of the study are listed and compared in Table 2.

However, presence of cardiovascular risk factors was correlated with HP infection ($P=0.022$, $r=0.171$). People with cardiovascular risk factors were more infected with HP than others. The frequency of men with HP infection was more than females among both cases and controls; but these differences were not statistically significant ($P>0.05$).

Odds ratios of risk factors for coronary heart diseases are shown in Table 3. The frequency of high fibrinogen level in patients with HP infection who had IHD was 14.3% (9 persons); and, in patients with HP infection without IHD was 14.3% (7 persons). This difference was not significant ($P>0.05$).

Conclusion

Recent evidence suggests that there may be a probable role of bacterial infections in IHD [20]. Some studies have shown the epidemiologic relation between HP and IHD [8,21]. However, this information was in doubt later [13,22-23]. Despite inability in showing the presence of HP in atherosclerotic plaques [24], chronic HP infection may be a risk factor for IHD with increase in fibrinogen level [25] or other unknown mechanisms [8, 26]. Some studies have expressed a strong significant association between HP and plasma fibrinogen concentration [3, 9].

A study on 317 patients referred for angiography showed that there was HP infection and

IHD in 127 cases (40%) simultaneously. Forty-nine patients from these 127 cases had a fibrinogen level more than 3.5 g/dl. There was not a significant relation between HP infection and IHD. However, the frequency of high fibrinogen level in cases with HP infection, with and without IHD, was 35.1% and 17.5% respectively [$OR=2(95\% CI: 0.9-4.6)$, $P=0.05$]. This odds ratio was only resulting from high fibrinogen level and by omission of the effect of other systemic inflammatory factors [10].

Another study on 84 patients with IHD who had HP and/or Chlamydia pneumonia infection with normal levels of acute phase reactants suggested that treatment of these infections cause a significant ($P<0.001$) decrease in fibrinogen level from 3.65 ± 0.58 to 3.09 ± 0.52 g/dl [20]. This study showed a significant ($P=0.01$) negative relation between fibrinogen level and age as well [20]. This study also showed an association between HP infection and fibrinogen level; but, the present study could not support it. Torgano et al [20] believed that indefinite results of the previous studies about the probable relation between HP infection and IHD may be due to considering HP as a single and separate infective factor till recently and not in association with other pathogens which can sometimes have a synergistic effect on its activity. Although, coexistence of antibody against Chlamydia pneumonia and HP in the general population is about 50% [27, 28], it is higher in patients with IHD [20].

The probable mechanism of association between HP, fibrinogen and IHD can be via stimulation of mononuclear cells which produce a tissue factor-like procoagulant activity that, through the extrinsic pathway of blood coagulation, converts fibrinogen to fibrin [29]. HP in-

fection can therefore have a direct effect on clotting mechanisms and lead to a prethrombotic state that predisposes to coronary artery disease.

However, Lee et al [30] declared that HP infection is not an independent risk factor for coronary heart disease, and it does not alter the coagulation system or evoke the systemic inflammatory response.

Some previous studies do not show satisfied results for proving or refusing a causal relation between HP and IHD. The main reasons may be the small sample size and absence of precise control of potential confounders in this association [5,31,32]. Researches with high sample size [13] and a meta-analysis [5] also believe that there is a moderate to weak association between HP and IHD and these studies reject any strong relation.

In the study, there was not a link between H. pylori infection, fibrinogen level and IHD. Although some limitations were seen in our study such as lack of frequency matching of age and weight in two groups of the study, but still the difference was not statistically significant.

Anyhow, if there was a relation or impact of infection on IHD, it should not be accepted hastily and moreover, precise evaluation by more sensitive and specific methods is needed. Clinical trials for treatment and eradication of HP in patients with IHD should be performed with suitable sample size, appropriate controls and correct methodology and must follow the patients for a long period of time.

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