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Hepatitis B virus infection and coronary atherosclerosis: Results from a population with relatively high prevalence of hepatitis B virus

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Abstract

AIM: To investigate the possible association between hepatitis B virus (HBV) infection and angiographically proven coronary artery disease (CAD) in a population with relatively high prevalence of HBV.

METHODS: Sera from 434 patients who underwent coronary angiography were tested for HBV antigens (HBsAg, HBeAg) and antibodies (Anti-HBs, Anti-HBc and Anti-HBe) by ELISA.

RESULTS: Seventy-seven percent (224/291) of the patients with CAD and 73.4% (105/143) of the patients without angiographic evidence of atherosclerosis were seropositive for HBV (P>0.05). However, C-reactive protein (CRP) levels were significantly higher in patients with CAD (P = 0.008), while lower in HBV seropositive population (P = 0.043 and P = 0.021 after adjustment for conventional risk factors).

CONCLUSION: Our results suggested HBV infection negatively correlates with CRP levels, but seems not to be associated with coronary atherosclerosis.

Key words: Coronary artery disease; Hepatitis B virus; C-reactive protein; Infection

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INTRODUCTION

As one of the most prevalent infectious disease worldwide[1], hepatitis B Virus (HBV) has been threatening the public health of the Chinese. Researches had revealed several abnormal immune responses in hepatitis B patients[2], which might further contribute other complications such as liver cirrhosis, hepatocellular carcinoma, *etc*., while it is still controversial whether these HBV induced inflammation status correlates with disease in organ other than liver.

A possible role for infections in atherogenesis has been deeply scrutinized since the demonstration of herpes virus-induced atherosclerosis in chickens in 1978[3]; however, the bulk of supportive evidence has been accumulated in the past few decades[4-7]. The results of several published studies suggested a link between infection with microorganisms such as bacteria, Chlamydia, pneumoniae[8-10], *Helicobacter pylori*[11-13], or Porphyromonas gingivalis[14,15] and with the viruses cytomegalovirus[16-18], herpes simplex virus[19,20], or hepatitis A virus[20,21], and an increased risk of cardiovascular and cerebrovascular diseases. However, the atherogenic effects of certain infective agents remain controversial[22-25]. Nevertheless, at present, assessment of possible associations between infective agents and the risk of atheromatous disease might be still useful for the identification of individuals at higher risk of future cardiovascular and cerebrovascular events.

We reasoned that HBV would be a rational candidate pathogen among stimuli that contribute to atherosclerosis. It shares almost all the characteristics of the infectious agents implicated in the development of atherosclerosis. For example, it is one of the intracellular pathogens and can produce persistent liver disease, establish long-term, persistent infection, which induce long-lasting effects on host, such as persistent circulating antibodies. In a recently published study from a health-screening test cohort, a strong association between HBsAg carrier and carotid atherosclerosis was reported[26]. Although the concept behind this association seems to be plausible and attractive, an accumulative collection of data is clearly required to confirm the hypothesis in a different study population. The high endemicity of HBV infection and liver disease in China mainland made it possible for us to assess whether coronary

atherogenesis was association of HBV serologic markers in a population with greater prevalence of HBV.

Substantial evidence now exists indicating that inflammation plays an important role in atherogenesis[27-30]. Accordingly, we used elevated serum levels of C-reactive protein (CRP) as a marker of an underlying inflammatory process and determined whether prior HBV infection was involved in inducing chronic inflammation.

Therefore, the aim of the present investigation was to test (1) whether the association between HBV infection and atherosclerosis still remained in a HBV-predisposed study population; (2) whether HBV infection was involved in triggering and sustaining the chronic inflammation process that had been proved to be critical in atherogenesis.

MATERIALS AND METHODS

Study subjects

A total of 434 patients of both genders were recruited at Zhongshan Hospital (Shanghai, China). Written informed consent was obtained from all study subjects, who approved the collection of blood samples for scientific research. The study cohort consisted of individuals referred for coronary angiography because of chest pain or noninvasive tests compatible with myocardial ischemia. We defined a patient as having coronary stenosis if there was an angiographic evidence of atherosclerosis; CAD with evidence of $\geqslant$50% stenosis of $\geqslant$1 major coronary artery by coronary angiography. Patients with myocardial infarction within previous 6 mo, valvular heart disease or nonatherosclerotic cardiomyopathy were excluded. Blood samples were taken for various measurements in these patients.

Atherosclerosis risk factors

Analyzed risk factors for atherosclerosis included age, sex, smoking (those who had stopped smoking 20 years ago and who were <30 years old when they stopped smoking were considered as non-smokers), diabetes (who were taking insulin, oral hypoglycemic agents, had previously received such treatment, or were currently using dietary modification to control the condition), hypercholesterolemia (who had a serum cholesterol value >6.2 mmol/L or were receiving cholesterol-lowering treatment), hypertension (who had received such a diagnosis with arterial pressure >140/90 mmHg or were being treated with antihypertensive medications or dietary modification.), family history and elevated CRP levels.

Laboratory testing

Serum samples obtained from all study subjects were frozen at -70 ℃, and aliquots were thawed when needed for specific tests. Serum antigens (HBsAg, HBeAg) and antibodies (anti-HBs, anti-HBc, anti-HBe) for HBV were measured by ELISA (HBV-kit, KeHua, China) according to the manufacturer's instructions. A quantitative ELISA was used to determine serum CRP (CRP-kit, DSL, USA). A set of CRP standards was used to plot a standard curve of absorbance *vs* CRP concentration from which the CRP concentrations in the unknown can be calculated.

Statistical analysis

Categorical data were analyzed by the χ^2 test (Fisher's exact test for small samples), with all tests double-sided. Analyses of CRP serum level in relation to HBV and other factors were made by the unpaired *t*-test between different groups as a continuous variable and further adjusted using partial correlation investigation. Estimated Pearson correlation value (*r*) was used to indicate the strength of the relationship. The covariates considered here included age, male sex, cigarette smoking, diabetes, hypercholesterolemia, hypertension and family history. Results for normally distributed continuous variables are expressed as mean±SD.

RESULTS

Study population

Four hundred and thirty four subjects were studied. Their ages ranged from 27 to 88 years (mean 62.2±10.36 years). There were 308 (71%) men and 291 (67.1%) with coronary atherosclerosis. All the traditional CAD risk factors (age, male sex, diabetes, hypertension and smoking) but hypercholesterolemia were also proved to be associated with the risk of CAD (Table 1). Besides, elevated CRP levels were demonstrated significantly higher in those with CAD compared to those without CAD (5.70±0.55 mg/L *vs* 3.23±0.37 mg/L, $P = 0.008$).

Table 1 Traditional risk factors and CAD

Characteristics	Frequency of factors%		*P*
	CAD (*n* = 291)	Non-CAD (*n* = 143)	
Age (yr)	63.05±10.46	59.48±10.43	0.005
Male Sex	78.7	57.4	<0.0001
Smoking	42.6	18.9	<0.0001
Diabetes	19.6	7.8	0.001
Hypertension	72.5	57.3	0.002
Hypercholesterolemia	25.8	21.7	0.351
Family history	12.9	11.9	0.877
CRP(mg/L)	5.70±0.55	3.23±0.37	0.008

HBV seropositivity and risk factors of CAD

HBV seropositive subjects were defined as samples with any of the five serological markers of HBV (HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc) proved to be positive. Of all the study population, there were totally 329 (75.8%) HBV-seropositive individuals, 22 (5.1%) positive for HBsAg, 213 (49.1%) for anti-HBs, 285 (65.7%) for anti-HBc, 2 (0.5%) for HBeAg and 93 (21.4%) for anti-HBe. Although seropositivity (Table 2) and most of the single HBV serological markers were not relative with any of the traditional factors respectively, anti-HBc was negatively associated with hypercholesterolemia ($r = -0.106$, $P = 0.025$, OR = 0.614, 95% CI 0.401-0.941).

CRP and HBV seropositivity

Mean CRP levels were lower in HBV seropositive (4.29±0.44 mg/L) than in HBV seronegative individuals (6.60±1.04 mg/L) ($r = -0.130$, $P = 0.043$). Individual serological markers such as anti-HBc and anti-HBs also relate to a low level of CRP

Table 2 Baseline characteristics of study population with or without HBV seropositivity

Characteristics	HBV seropositive (n = 329)	Non-HBV seropositive (n = 105)	P
Age (yr)	62.12±10.06	62.49±11.18	0.290
Male (%)	70.2	73.3	0.622
Smoking (%)	32.8	40.9	0.158
Diabetes (%)	14.6	15.2	0.515
Hypertension (%)	62.3	64.8	0.812
Family history (%)	13.7	7.6	0.123
Hypercholesterolemia (%)	21.6	22.9	0.787

Table 3 Association between HBV serological markers and CRP level

HBV serological markers	Pearson correlation (r)	P	P^1
HBsAg	-0.036	0.511	0.406
Anti-HBs	-0.126	0.027	0.029
HbeAg[2]	0.000	1	1
Anti-HBe	-0.014	0.795	0.643
Anti-HBc	-0.115	0.049	0.032
HBV seropositive	-0.130	0.043	0.015

[1]After adjustment for smoking. [2]Fisher's exact test was used.

(Table 3). Besides smoking age, male sex and hypertension, *etc.* was shown to be associated with the increased CRP level (r = 0.108, P = 0.039) as reported previously[24]. However, the significant association between elevated CRP levels and HBV seropositivity maintained after adjustment for smoking (P = 0.015).

HBV seropositivity and CAD

The HBV seropositive as well as single HBV serological marker was not significantly related with CAD (Table 4). Other stages of infection inferred by serological test such as healthy carriers (with HBsAg, anti-HBc and anti-HBeAg positive) (r = -0.052, P = 0.262), resolved HBV infection (with anti-HBs, anti-HBc and anti-HBe positive) (r = 0.037, P = 0.421) and HBsAg-negative HBV infection (anti-HBc positive only) (r = 0.019, P = 0.676) showed no significant correlation with CAD either.

In addition, since the HBV seropositivity was proven to be negatively associated with CRP level in our study population, we further analyzed two subgroups of patients (one with CRP levels at or below the median and the other with CRP values above the median) to try to exclude the influence on the association of HBV seropositivity and CAD from its interaction with CRP levels. The estimated pearson correlation value were 0.034 and -0.051 respectively with both P>0.05.

DISCUSSION

So far there is still few data available to prove the association between HBV infection and atherogenesis. Kiechl *et al*[31] found no significant association between chronic hepatitis and the development of new carotid atheromatous plaques, although they did not specify the type of hepatitis virus. However, another study in Japan demonstrated an increased prevalence of carotid atherosclerosis in HBV carriers[26].

Table 4 HBV serological markers and CAD

HBV serum factor	Positive frequency of factors (%)		P
	CAD	Non-CAD	
HbsAg	4.5	6.3	0.415
Anti-HBs	49.8	46.9	0.560
HbeAg	0.7	0	1.000
Anti-Hbe	22.0	21.7	0.969
Anti-HBc	69.4	59.4	0.066
Healthy carriers[1]	2.8	4.9	0.270
Resolved HBV infection[2]	11.7	9.1	0.474
HBsAg (-) HBV infection[3]	16.8	15.4	0.700
HBV seropositive	77.0	73.4	0.417

[1]Healthy carriers: HBsAg (+), anti-HBc (+) and anti-HBeAg (+). [2]Resolved HBV infection: anti-HBs (+), anti-HBc (+) and anti-HBe (+). [3]HBsAg (-) HBV infection: anti-HBc positive only.

Differences in study design, frequency of individuals with chronic HBV infection, and possibly region differences might explain the difference results of their study and ours.

Since serologic markers of HBV provide tools to follow the natural course of the disease and hitherto, there were no concrete evidence supporting the infection of HBV in endothelial cells, we examined the five widely used serologic markers instead of more sensitive HBV-DNA detection with the hypothesis that circulating HBV-associated antigens and antibodies might be the risk factors for atherogenesis. In our investigation, we found no evidence to support an association of HBV seropositivity and CAD prevalence. Subgroups used in clinic such as healthy carriers, those resolved HBV infection and those with HBsAg-negative HBV infection did not show correlation to coronary stenosis either, despite suggestive evidence from some clinical reports[32] and plausible mechanisms[33-35].

Although HBV seropositivity failed to be relative with CAD prevalence, one observation needed emphasis in this study. anti-HBs, anti-HBc and HBV seropositivity were all negatively related with elevated CRP levels, which were independent of other risk factors for atherosclerosis (Table 3). As CRP had been suggested as a cardiovascular risk factor, all these results hinted a possible protective trend of HBV on atherogenesis derived from a study in HBV high-risk region. This tendency is quite interesting and might be expected through several possible evidences: (1) HBV infection is highly prevalent in China and some developing regions compared to European countries; in contrast, the incidence of cardiovascular diseases is remarkably higher in Europe; (2) In general, the clinical course of chronic HBV infection may lead to hepatic decompensation, progression of liver disease, and the development of cirrhosis. It was reported that liver cirrhosis appears to be associated with a decreased risk of atherosclerosis, which may be attributed to the reduction of some traditional risk factors for atherosclerosis, such as high lipoprotein A and total cholesterol[36]. It is reasonable to hypothesize that the expression of CRP, a liver-specific protein, may also be influenced by hepatic dysfunction during chronic HBV infection; (3) A recent study demonstrated that there was no relationship between HBV carrier or seropositivity and increased pulse wave velocity, which suggested HBV

infection did not seem to be able to contribute to increase arterial stiffness. Although it was reported by Ishizaka *et al*[26] that HBsAg seropositivity was a risk factor for carotid atherosclerosis, which was not associated with CRP level, the conclusion might be limited by the relatively low prevalence of HBV carriers (0.9%) in that population, compared to 5.1% seropositivity for HBsAg in this study.

There are several caveats relating to our study that must be noted. First, the study design was cross-sectional in nature, which cannot establish causality. It can only establish an association. Therefore, any conclusion derived from such study must be considered preliminary and hypothesis-generating, rather than hypothesis-proving. Second, the present study is relatively small in size. As a result, we may have missed a very weak association between HBV seropositivity and coronary stenosis. Nevertheless this study is one of the largest studies on HBV infection and CAD to date. Third, the individuals of control group might still be consisted of suspected CAD who may not be representative of other individuals without clinical features triggering the decision to perform coronary angiography. Fourth, the effects of reducing the CRP levels, a widely accepted atherosclerosis risk, in HBV seropositive population, might cover the relationship between HBV seropositivity and coronary atherosclerosis.

In conclusion, our results indicated that there is no statistical relationship between HBV infection and coronary atherosclerosis. We disagree with previously reported findings[26] that hepatitis B infection is probably an important contributor to CAD. And the role of HBV-associated reduction of CRP levels during the development of coronary atherosclerosis is still a disputed issue.

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