Chronic Hepatitis B Virus Infection and Dyslipidemia

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Background and Purpose: The association of chronic hepatitis B virus (HBV) infection and decreased levels of high-density lipoprotein cholesterol (HDL-C) has been well documented. However, the relationship between dyslipidemia and asymptomatic chronic HBV infection is still unclear.

Methods: In 1997, 1330 medical center employees (405 men and 925 women) were recruited to evaluate the effects of chronic HBV infection on serum lipid profile, including total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol, and triglycerides (TG). Among these patients, 195 were found to have chronic HBV infection and 35 (17.9%) of them were found to have elevated alanine aminotransferase (ALT). Multiple linear regression analyses were used to evaluate the effects of chronic HBV infection on serum lipids.

Results: The most significant finding was that levels of TC and HDL-C were decreased by 5.8 and 2.7 mg/dL respectively, among patients with asymptomatic chronic HBV infection (serum ALT < 40 U/L). After controlling for other determinants, male gender, old age, higher body mass index (BMI) and waist-to-hip ratio, current smoking, and hepatitis B surface antigen-negative status with ALT ≥ 40 U/L were associated with lower serum HDL-C and higher TG levels. However, moderate to heavy alcohol drinking, physically active lifestyle, and lower BMI were associated with higher levels of HDL-C.

Conclusions: Asymptomatic chronic HBV infection was associated with lower serum levels of TC and HDL-C. Elevation of ALT was also an indicator of lower levels of HDL-C in patients with chronic hepatitis B and lower serum HDL-C and higher TG levels in patients without HBV infection. These findings also indicated the need to monitor the risk of atherosclerotic diseases in patients with asymptomatic chronic HBV infection, especially those with lower HDL-C levels.

Key words: Alanine aminotransferase; Hepatitis B virus; Dyslipidemia; Lipoprotein, HDL cholesterol

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Hepatitis B virus (HBV) infection with its high prevalence and associated morbidity and mortality has been recognized as an important health issue in Taiwan for more than 3 decades.[1] The hepatitis B surface antigen (HBsAg) infection rate in the general population is about 10 to 20% in Taiwan.[1,2] Hepatoma results in about 5800 deaths and was the leading cause of cancer death in Taiwan in 1999.[3] People with chronic HBV infection are at risk for developing sequelae, including chronic active hepatitis,[4] cirrhosis,[5] and hepatocellular carcinoma.[6]

Chronic hepatitis B and C and cirrhosis of the liver have been associated with impaired lipid metabolism, reduced total cholesterol (TC), and reduced high-density lipoprotein cholesterol (HDL-C) in case-control studies.[7,8] Changes in serum lipids were commonly found in patients with chronic liver disease,[7–9] and a study in China found that prolonged HBV infection was related to low blood cholesterol concentration and increased frequency of liver cancer.[10] However, the status of serum HDL-C in patients with asymptomatic chronic HBV infection has not been reported. Furthermore, most studies about the influence of blood lipids in patients with hepatitis were conducted in small series[7–9] except for a study from China,[10] and the potential confounding factors of blood lipid levels were often overlooked,[7,8] or only partially adjusted.[9,10]

We conducted this study to delineate the effects of HBV infection status and elevation of alanine aminotransferase (ALT) levels on serum lipid profile, especially their association with dyslipidemia (lower levels of HDL-C and/or higher levels of triglyceride).

Methods

Subjects

In 1997, 1693 health workers in a medical center aged 30 to 65 years were invited to receive an annual

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physical examination, which included a general health survey questionnaire, collection of blood for serum lipid profile (TC, triglycerides [TG], HDL-C, and low-density lipoprotein cholesterol [LDL-C]), hepatitis B and C markers, and associated biochemical tests. Among them, 260 subjects with incomplete questionnaires, 57 with incomplete data on hepatitis markers, and 25 with previously identified clinical conditions that may affect lipid profile were excluded. In addition, 21 subjects with TG > 400 mg/dL were excluded due to the limitations of the LDL-C calculation by Friedewald's formula.[11] Finally, 405 men and 925 women were included in this study (78.6%).

Baseline information and medical history

Information about age, gender, type of work, lifestyles (smoking and alcohol drinking), medication history, physical activities (including leisure-time and working), and medical and family histories of major diseases was obtained through a self-reported questionnaire, and later verified through checking of medical charts. Body weight and height, waist-to-hip ratio (WHR), and blood pressure (BP) were measured during the physical examination.

BP measurements were performed with a mercury sphygmomanometer in a standardized fashion. BP was recorded using the mean of 2 measurements taken after 5 minutes of rest in the sitting position. Hypertension was defined according to the criteria established by the Fifth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V). Diabetes mellitus (DM) was defined as fasting glucose ≥ 140 mg/dL, and/or a history of use of oral hypoglycemic agents or insulin injection. Body mass index (BMI) was calculated as weight (in kg) divided by height (in meters) squared. Individuals with BMI ≥ 25 kg/m^2 were considered as overweight.

Physical activity index was calculated using the methods of Paffenbarger et al,[12] and computed as an estimate of energy expended in walking, climbing stairs, playing sports, yard work, and so on.[13] Data on alcohol use and smoking were self-reported on the questionnaire. Amount of alcohol consumed was calculated based on data obtained on frequency and amount, and was summarized as average number of alcoholic drinks consumed per week. An extent of alcohol drinking of 100 to 367.6 g/week was considered a moderate to heavy amount and > 367.6 g/week was considered excessive, as modified from the definition by Lee et al in a study conducted in Taiwanese.[14] Family history of premature coronary heart disease was indicated by the occurrence of myocardial infarction or sudden death before 55 years of age of an individual's father or other male first-degree relative, or before 65 years of age of the mother or other female first-degree relative.

Lipid levels, liver function profile and viral hepatitis markers

Blood samples from patients who had fasted 10 to 14 hours overnight were drawn from the antecubital vein for lipid and glucose determinations with the patient in a seated position. Serum levels of lipids, including TC, HDL-C, and TG were assayed in the central laboratory of National Taiwan University Hospital.[15] The TC and TG levels (determined by enzymatic methods described elsewhere) were measured with an automatic multichannel chemical analyzer (Hitachi 7450; Hitachi Corp., Tokyo, Japan). HDL-C level was determined by measuring cholesterol in the supernantant after precipitating very low-density lipoprotein cholesterol and LDL-C with Mg^{2+}/phosphotungstate reagent. LDL-C was calculated from Friedewald's formula.[11] Liver function profile, including serum aspartate aminotransferase (AST), ALT, bilirubin, albumin, and globulin were also determined using routine enzymatic methods. Data on hepatitis markers were collected from chart review and HBsAg and anti-hepatitis C virus (anti-HCV) antibody were rechecked for every participant using radiommunoassays.

Statistical methods

In the data analysis, characteristics and cardiovascular risk factors of study subjects were first compared by hepatitis status, i.e., between HBsAg-positive (+) and -negative (–) status, and between anti-HCV (+) and (–). Variables in interval scales were summarized as the mean ± standard deviation (SD). The categorical data on alcohol and smoking habits were expressed as a percentage of positivity. Both *t* test and ANOVA test were used to make comparisons among these groups.

Multiple linear regression analyses were used to evaluate the determinants of lipid profile and estimate the magnitudes of effects. Because there were only 32 subjects with hepatitis C infection, we excluded these subjects and another 2 cases with coinfections of hepatitis B and C from the multivariate regression analysis.

The presence or absence of HBsAg (+) or (–) and status of liver function (serum ALT ≥ 40 U/L or ALT < 40 U/L) were included to test their contribution to lipid profile. An asymptomatic chronic HBV infection was defined as a positive HBsAg and a normal ALT level (defined as serum ALT < 40 U/L). Serum albumin level was also treated as a potential confounding factor that might affect the relation between hepatitis and lipid profiles. All statistical analyses were performed with SAS statistical software (Version 8.0, SAS Institute, Cary NC, USA). A p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The prevalence of HBsAg (+) was 17.8% in men and 13.4% in women; anti-HCV (+) status was found in 3.7% of men and 1.9% of women. Table 1 summarizes the reasons for secondary dyslipidemia or decompensated liver disease in 25 excluded cases. The characteristics of subjects with and without hepatitis B or C infection are summarized in Table 2. Compared to those without hepatitis B infection, subjects with HBsAg (+) were largely male, had lower levels of TC, HDL-C, and a higher prevalence of abnormal liver function (defined as levels of ALT ≥ 40 U/L). Among patients with chronic HBV infection, 17.9% had elevated ALT levels. Compared to those without hepatitis C infection, subjects with anti-HCV (+) status were largely male, older, more obese (higher BMI and WHR), and had a higher prevalence of abnormal liver function.

Table 1. Clinical conditions and laboratory findings that may affect lipid profile in excluded subjects.

Condition	No. of cases
Clinical conditions*	
Pregnancy	12
Hyperthyroidism	3
Chemotherapy	1
Steroid use	1
Laboratory findings†	
Albumin < 3.5 g/dL	4
Total bilirubin > 2 mg/dL	4
Total	25

* Clinical conditions associated with secondary dyslipidemia.
† Laboratory findings that define decompensated liver disease or poor nutrition status.

Effects of chronic hepatitis B infection and elevated ALT

After controlling for potential confounding variables, multiple linear regression analyses showed that asymptomatic chronic HBV infection was correlated with lower TC (-5.8 mg/dL) and HDL-C (-2.7 mg/dL) levels, as shown in Table 3.

However, only a moderate reducing effect on serum HDL-C (-2.3 mg/dL) was found in patients with chronic hepatitis B, defined as HBsAg (+) with ALT ≥ 40 U/L lasting at least 6 months. Those with HBsAg (–) and abnormal liver function, defined as ALT ≥ 40 U/L, had lower HDL-C (-2.9 mg/dL) and higher TG (+35.4 mg/dL) levels. Serum albumin levels showed no significant association with serum lipids (Table 3).

Effects of cardiovascular risk factors

Table 3 shows that men and older subjects (≥ 40 years old) had significantly higher TC, LDL-C and TG levels, and lower HDL-C levels. Subjects with higher BMI, WHR, and current smokers of more than 0.5 packs per day (PPD) were associated with lower serum HDL-C and higher TG levels. A family history of premature coronary heart disease was associated with a higher LDL-C level.

However, subjects with moderate to heavy alcohol drinking and subjects who were physically active (defined as physical activity > 3000 kcal/week) were associated with increased HDL-C levels of 3.5 mg/dL and 1.6 mg/dL, respectively. Subjects with DM had a higher TG level and a trend to lower levels of HDL-C. Patterns of diet intake in HBsAg (+) patients were not significantly different from HBsAg (–) patients, and this variable was therefore not included in the multiple linear regression analysis model.

Table 2. Characteristics of subjects with and without hepatitis B or hepatitis C infection.

Characteristic*	HBsAg (+) (n = 195)	HBsAg (–) (n = 1135)	Anti-HCV (+) (n = 32)	Anti-HCV (–) (n = 1298)
Age (years)	40.44 (7.54)	41.12 (8.25)	48.13 (7.81)	40.85 (8.08)‡
Male (%)	36.9	29.3†	43.8	30.1†
Current smoker (%)	8.7	6.9	3.1	7.2
Alcohol habit (%)‡	9.2	6.3	3.1	6.9
ALT ≥ 40 U/L (%)	17.9	6.9‡	25.0	8.1‡
Body mass index (kg/m^2)	23.54 (3.24)	23.45 (3.12)	24.80 (3.59)	23.43 (3.12)†
Waist-to-hip ratio	0.86 (0.08)	0.85 (0.07)	0.89 (0.05)	0.85 (0.07)‡
Physical activity index (/1000 kcal/week)	3.09 (1.61)	3.24 (1.43)	3.55 (1.45)	3.21 (1.46)
TC (mg/dL)	181.7 (29.8)	186.8 (33.3)†	187.9 (35.2)	186.0 (32.9)
HDL-C (mg/dL)	53.4 (11.6)	56.5 (13.5)‡	54.9 (15.1)	56.1 (13.1)
LDL-C (mg/dL)	108.7 (25.9)	109.4 (28.6)	108.3 (26.3)	109.4 (28.2)
Triglyceride (mg/dL)	99.2 (54.0)	102.7 (57.6)	125.8 (71.7)	101.9 (56.7)†
Fasting sugar (mg/dL)	92.2 (24.7)	91.0 (17.5)	91.8 (17.6)	91.1 (18.7)

* Values are presented as mean (SD), except gender, current smoker, alcohol habit and ALT ≥ 40 U/L. Alcohol habit means alcohol consumption ≥ 100 g/week.
† $p < 0.05$.
‡ $p < 0.01$.
ALT = alanine aminotransferase; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

Table 3. Multiple linear regression analyses to evaluate the predictive effects of viral hepatitis B infection and other determinants on serum lipid profile.

Variables	Lipid profile (mg/dL)							
	TC		HDL-C		LDL-C		Triglyceride	
	β†	*p*	β†	*p*	β†	*p*	β†	*p*
Intercept	155.8		68.8		88.9		-11.5	
Male gender	5.4	0.02	-7.0	< 0.01	9.7	< 0.01	14.2	< 0.01
Age ≥ 40 *vs* < 40 years	12.8	<0.01	2.3	< 0.01	8.1	< 0.01	10.6	< 0.01
BMI (kg/m^2) *vs* 23–24.9								
< 23	-4.6	0.04	5.0	< 0.01	-7.0	< 0.01	-13.3	< 0.01
≥ 25	1.9	0.41	-2.7	< 0.01	0.8	0.81	22.1	< 0.01
WHR	22.8	0.11	-15.1	< 0.01	16.2	0.19	109.8	< 0.01
Current smoker *vs* non-smoker or ex-smoker								
< 0.5 PPD	-0.0	1.00	-1.2	0.48	2.7	0.53	-7.1	0.35
≥ 0.5 PPD	0.8	0.88	-4.3	0.02	-1.2	0.81	31.0	< 0.01
Alcohol (g/week) *vs* non-drinker								
100–367.5	0.4	0.93	3.5	0.03	-4.3	0.24	2.7	0.34
> 367.5	-7.0	0.32	2.3	0.38	-11.2	0.07	8.9	0.42
Physical activity *vs* < 3000 kcal/week	1.5	0.38	1.6	0.02	0.8	0.57	-4.4	0.13
Hypertension	-0.1	0.97	0.4	0.62	-0.4	0.82	-0.2	0.96
Diabetes mellitus	-1.2	0.86	-3.9	0.053	-1.5	0.72	23.9	< 0.01
Family history*	9.3	0.01	-0.2	0.90	10.1	< 0.01	-2.7	0.65
Albumin (g/dL)	0.8	0.23	-0.2	0.50	0.8	0.29	1.8	0.07
Hepatitis B status *vs* HBsAg (–) and ALT < 40 U/L								
HBsAg (+) and ALT ≥ 40 U/L	-0.8	0.88	-2.3	0.02	3.5	0.46	-8.9	0.28
HBsAg (+) and ALT < 40 U/L	-5.8	0.04	-2.7	< 0.01	-2.7	0.24	-0.9	0.80
HBsAg (–) and ALT ≥ 40 U/L	-0.4	0.92	-2.9	< 0.01	-3.9	0.27	35.4	< 0.01
R^2	0.08		0.23		0.09		0.26	

* Family history means family history of premature coronary artery disease.
† β means regression coefficient.
BMI = body mass index; WHR = waist-to-hip ratio; PPD = packs per day; HBsAg = hepatitis B surface antigen; ALT = alanine aminotransferase; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Discussion

To our knowledge, this study is the first to document that asymptomatic chronic HBV infection has a significant effect in lowering HDL-C and TC. The additional finding of decreased serum levels of HDL-C in chronic hepatitis B in this study is compatible with previous studies.[7,8] Because most of the measured HDL-C is synthesized in the liver,[16] major injuries to hepatocytes, such as those caused by alcohol consumption, chronic viral hepatitis or cirrhosis of liver, might produce abnormal liver function and moderate decrease in levels of HDL-C and TC.[7,8] In patients with chronic liver disease, the lower level of cholesterol indicated the severity of liver cell injury, which was associated with impairment of the synthetic ability of the liver.[17]

Male gender, old age,[18,19] obesity,[20] and DM[21] were reported to be associated with dyslipidemia among Caucasians. This study had similar findings, as shown in Table 3, which corroborated the above hypotheses in ethnic Chinese from our previous studies.[22,23] The lower HDL-C and higher TG levels in subjects with current smoking ≥ 0.5 PPD is similar to previous findings.[24] This and other studies have observed that alcohol drinkers have higher HDL-C levels than non-drinkers,[25] and physically active subjects had higher levels of HDL-C.[26] All of these consistent findings strongly support the validity of this study.

The detailed mechanism responsible for the HDL-C-reducing effect of chronic HBV infection remains to be elucidated. An enzyme involved in the biotransformation of HDL, lecithin-cholesterol acyltransferase (LCAT), was reported to be reduced in patients with advanced chronic liver disease or cirrhosis, probably because of impaired hepatic synthesis.[7,27,28] This reduction may also decrease HDL-C and TC in the case of mild hepatic damage that is not reflected in serum ALT level. Since our study did not perform abdominal sonography or measure hepatitis B e antigen, we could not differentiate the exact clinical stage of the HBV infection for each patient, which limits the inference potential of this study.

Lipids have been considered to play an important role in the host immune response to infections.[29] Lipoproteins can bind a variety of viruses and reduce their toxic effect.[30] Thus, decreased levels of TC and HDL-C in patients with asymptomatic chronic HBV infection may reduce their antiviral response. Because an association between low levels of cholesterol and liver cancer has been observed in chronic HBV infections,[10]

patients with asymptomatic chronic HBV infection with decreased HDL-C and TC should be followed due to their increased risk of developing liver cancer in the future.

A previous study showed that elevated ALT was associated with higher levels of BMI, glucose, and uric acid in a large cohort of 8501 men and women with hyperlipidemia, and this combination of clinical features was designated as plurimetabolic syndrome.[31] High ALT is also associated with impaired insulin sensitivity and is a predictor of type 2 DM.[32] Elevation of ALT in non-alcoholic subjects without HBV and HCV infections is often associated with liver steatosis, which had a strong relationship with obesity, DM and hypertriglyceridemia in a previous study.[33] In this study, we demonstrated an association between elevated serum levels of ALT and lower levels of HDL-C in patients with HBsAg (+), and lower levels of HDL-C and higher levels of TG in patients with HBsAg (–). These findings suggest that liver steatosis and a clustering of symptoms indicative of a metabolic syndrome might be the cause of elevated ALT levels.

Dyslipidemia (lower HDL-C levels and/or higher TG levels), defined as the major component of metabolic syndrome according to the NCEP-ATP III,[34] was strongly associated with HBV infection and elevated ALT levels in this study. Dyslipidemia is also well known as a major risk factor for cardiovascular disease (CVD).[34] Thus, measurements of HBsAg markers and serum ALT levels at the time of health examinations could provide valuable information, especially in subjects at increased risk for CVD.

Clinical and experimental trials have shown that decreased levels of HDL-C increase the risk of CVD.[35,36] A hospital-based study in Taiwan also revealed that a lower HDL-C level was an important independent risk factor for coronary artery disease in patients with low serum TC and TG levels.[15] Low serum HDL-C level was also found to be associated with subclinical left ventricular systolic dysfunction in Chinese patients with stable angina whose serum levels of TC and TG were relatively low.[37] A recent study demonstrated HBsAg (+) was positively associated with carotid plaque with an odds ratio of 1.57 (95% CI, 1.10 to 2.24) compared with HBsAg (–), which may suggest a possible role of chronic HBV infection in the pathogenesis of carotid arteriosclerosis.[38] Chronic infection and inflammation have been suggested to be associated with atherosclerotic disease in recent studies.[39,40] Thus, the long-term effect of lowering levels of HDL-C in patients with chronic HBV infection deserves further investigation.

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