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Original Article

Differences in Hematological Characteristics, Including Cholesterol and Apolipoprotein B and E, between Hepatitis B Virus and Hepatitis C Virus Patients in Korea

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Hepatitis B virus (HBV) and hepatitis C virus (HCV) chronically cause hepatitis, liver cirrhosis, and hepatocellular carcinoma, and biomarkers related to liver damage are elevated in HBV and HCV patients. However, comparisons of biomarkers between HBV and HCV patients have not previously been reported. The aim of this study was to investigate differences in hematological biomarker in the sera of HBV and HCV patients and to find a key biomarker to differentiate between HBV and HCV infections. HBV (n=115) and HCV (n=128) samples (serum and whole blood) were collected and tested using a biochemical analysis system. The obtained data were analyzed with SPSS 18.0 statistical software. The mean age of the HCV group (60.3±14.1) was much higher than that of the HBV group (51.1±12.4). Male and female rates were 71.3% and 28.7% in the HBV group and 53.9% and 46.1% in the HCV group, respectively ($p = 0.005$). AST, ALT, and TG values were higher in the HCV group than in the HBV group. Although γ-GTP and LDL levels were higher in the HBV group than in the HCV group, apoB and apoE levels were much higher in HCV group than in HBV group ($p < 0.001$). There were no significant differences in the other hematological biomarkers between the HBV and HCV groups. In conclusion, HBV rates were higher in male patients, and HCV rates were higher in older patients. In particular, apoE and apoB were more highly expressed in HCV patients, and they might be key markers to differentiate HCV infection.

Key Words: Hepatitis B virus, Hepatitis C virus, Hematological biomarker, Apolipoprotein B & E

INTRODUCTION

Hepatitis refers to inflammation of the liver. Many factors can cause hepatitis, such as microorganism infection, certain drugs, organic solvents, and heavy alcohol use. Viruses are the most common cause of hepatitis in the world, and hepatitis A, B, C, D, and E virus (HAV, HBV, HCV, HDV, and HEV) are known as the most common causes of viral hepatitis. Hepatitis A and E are typically contracted by eating contaminated food or water. According to the World Health Organization (WHO), about 20 million people are infected

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with HEV and 1.4 million with HAV every year; however, the mortality rate is low and the disease ultimately resolves. Hepatitis B and C are usually transmitted through contact with infected body fluids, especially blood, and chronically, they can lead to liver cirrhosis and hepatocellular carcinoma. According to the WHO, more than 1 million people die each year due to HBV and HCV. HDV, known as delta virus, is an incomplete virus and requires the helper function of HBV (1~3).

In the field of public health, it is important to manage these viral diseases throughout the world, especially hepatitis B and C. There is no specific treatment for acute hepatitis B. Chronic hepatitis B can be treated with antiviral agents, but the treatment does not cure hepatitis B infection completely. Furthermore, treatment can be costly, due to the long period of treatment. Therefore, the WHO recommends vaccinations to prevent hepatitis B for all infants at birth. HBV prevalence is increasing in Korea, with an increasing number of new acute stage patients. On the other hand, HCV occur in about 3% of the world population and its chronic state develops in about 70% of infected patients. Chronic HBV develops in about 15% of infected patients. While there are several antiviral agents available to treat both acute and chronic hepatitis C, there is no vaccine. In Korea, about 4,000 patients suffer from HCV (1~3).

Many studies have been conducted on the pathogenesis of HBV and HCV in order to develop treatments. When HCV infects a hepatocyte, it has a strong relationship with cholesterol, especially low-density lipoprotein (LDL) cholesterol and apolipoprotein. Apolipoprotein E (apoE) is one of the plasma proteins that participates in the transport of cholesterol and other lipids, and some *in vitro* studies have suggested that it has a role in transporting HCV viral particles to hepatocytes (4~6). The apoE genotype has a strong association with some diseases; for example, family type III hyper lipoproteinemia is associated with the apoE ε2 allele, and high cholesterolemia, coronary artery disease, and Alzheimer's disease are associated with the apoE ε4 allele.

The mechanism of HBV infection is not clear, and hematological characteristics such as cholesterol are not completely known, except biomarkers associated with liver damages. However, HBV has a strong relationship with the oncogenic signaling pathway, which causes carcinoma (7, 8).

Therefore, at the point of relationship with HCV and apoE, we compared differences in hematological characteristics in the sera of HBV and HCV patients and sought to find a key biomarker to differentiate between HBV and HCV infections. In particular, we compared apolipoproteins by quantity of apolipoproteins and apoE genotype in patients with HBV and HCV.

MATERIALS AND METHODS

Clinical samples

HBV (n=115) and HCV (n=128) samples (serum and whole blood) were collected at Bundang Jaesang Hospital in 2012-2013. HBV patients were defined by the HBsAg test and HCV patients were defined by the anti-HCV test. Samples were stored immediately at -70℃. Clinically healthy persons (n=100), 45~60 years old, were selected as healthy controls. Medical records were collected to analyze the patients' hematological characteristics. This study was approved by the Institutional Review Board of Bundang Jaesang Hospital.

Quantitative analysis of apolipoprotein B and E

Apolipoprotein B Human ELISA kit and Apolipoprotein E Human ELISA kit (Abcam, United States) were used for serum analysis, following the kit protocol precisely.

ApoE genotyping

DNA was isolated from whole blood using a DNA isolation kit (Cosmogenotech, Seoul, South Korea). Isolated DNA was used for apoE genotyping using an EzWay™ Direct ApoE Genotyping kit (Komabiotech, Seoul, South Korea), which is based on the multiplex PCR method. Genotype was determined by electrophoresis in 2% agarose gel.

Statistical analysis

SPSS 18.0 statistical software was used for data analysis. Continuous variables such as hematological characteristics were compared with Student's *t*-test. Categorical variables

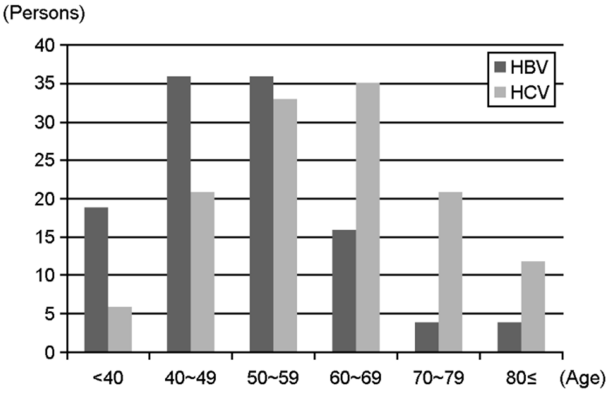

Figure 1. Distribution of HBV and HCV patients according to age.

Table 1. Comparison of age and gender between HBV and HCV patients

Characteristics	HBV (n=115)	HCV (n=128)	*p*
Age (mean ± SD)	51.1±12.4	60.3±14.1	0.000[a]
Gender (n, %)			
Male	82 (71.3)	69 (53.9)	0.005[b]
Female	33 (28.7)	59 (46.1)	

[a] Analyses of Student's *t*-test
[b] Analyses of cross-tabulation test

such as gender by hepatitis virus and apoE genotype were compared with a cross tabulation test.

RESULTS

The mean age of the HCV patients (60.3±14.1 years) was much higher than that of the HBV patients (51.1±12.4 years) ($p < 0.000$). The distributions of the HBV and HCV patients according to age followed a parallel pattern: most of the HBV patients were in their 40s and 50s, and most of the HCV patients were in their 50s and 60s (Fig. 1). The percentages of male and female HBV patients were 71.3% and 28.7%, and the percentages of male and female HCV patients were 53.9% and 46.1% (Table 1).

Both HBV and HCV patients had higher AFP, AST, ALT, ALP, γ-GTP, apoB, and apoE values compared with the normal control group. In particular, apoB and apoE levels were statistically significantly higher in the HBV patients ($p < 0.05$) and apoE levels were significantly higher in the HCV patients ($p < 0.000$). Total cholesterol, HDL, and LDL levels were lower in the HBV patients ($p < 0.005$, LDL $p < 0.05$, respectively) and TG levels were higher in the HCV patients.

The AST, ALT, and TG levels of the HCV patients were quite a bit higher than those of the HBV patients. While γ-GTP and LDL levels were higher in the HBV patients than in the HCV patients, apoB and apoE levels were almost twice as high in the HCV patients as in the HBV patients ($p < 0.005$). There were no significant differences in the other hematological characteristics between the HBV and HCV patients (Table 2).

The apoE genotype distribution results showed that in both the HBV and HCV patients, most genotypes (70%) were ε3/ε3. In particular, ε3/ε3 had the highest distribution (80%) in the HCV patients. Heterotypes such as ε2/ε3, ε2/ε4, and ε3/ε4 are more common in HBV patients. ε2/ε2 and ε4/ε4 were not found in this study (Table 3). Comparing apoE gene allele distribution in the HBV and HCV patients, ε3 was more common in the HCV patients (89.1%) than HBV patients (84.3%) and ε2 and ε4 was distinctly more common in the HBV patients (each 8.3%, 7.4%) than HCV patients (both 5.5%) (Table 4).

In the HBV patients, the ε3/ε3 group had higher AFP and ALP levels than the ε2/ε3 apoE genotype group and the ε2/ε3 group had higher AST and ALT levels than the ε3/ε3 apoE genotype group. In the HCV patients, the ε2/ε3 and ε3/ε3 apoE genotype groups had the same levels of AFP, ALP, AST, and ALT.

The ε3/ε3 group in the HBV patients and the ε2/ε3 group in the HCV patients had higher levels of γ-GTP. The ε2/ε3 group in the HBV patients and the ε3/ε3 group in the HCV patients had higher levels of TG. The ε2/ε3 group in the HCV patients and the ε2/ε4 group in the HBV patients had the lowest LDL levels. HDL levels were generally low when not accounting for apoE genotype or hepatitis type. In both the HBV and HCV patients, apoB levels were higher in the

Table 2. Comparison of hematological characteristics between HBV and HCV patients

Characteristics (unit)	HBV	HCV	Control	p^a	p^b	p^c
AFP (ng/ml)	94.7±597.8	79.1±406.9	2±1.1	0.790	0.745	0.843
Total protein (g/dl)	7.2±0.7	7.4±0.7	6.8±1.6	0.411	0.125	0.012
Albumin (g/dl)	4.0±0.5	4.0±0.6	4.4±0.1	0.353	0.352	0.862
AST (IU/l)	50.3±75.8	59.4±65.6	21.4±4.6	0.233	0.070	0.317
ALT (IU/l)	42.3±65.9	48.6±51.6	16.5±3.6	0.220	0.052	0.406
Total bilirubin (mg/dl)	1.7±4.2	1.1±1.6	0.8±0.3	0.688	0.802	0.110
ALP (IU/l)	301.9±256.5	303.1±216.0	242.5±46.3	0.646	0.578	0.971
γ-GTP (IU/l)	89.9±167.4	77.5±125.8	19.2±6.4	0.187	0.148	0.551
BUN (mg/dl)	17.2±9.5	19.4±14.9	16.2±3.6	0.840	0.670	0.183
Creatinine (mg/dl)	1.325±1.6	1.329±1.2	0.954±0.1	0.465	0.326	0.982
TG (mg/dl)	112.9±69.7	122.4±8.8	112±66.9	0.970	0.720	0.444
Total cholesterol (mg/dl)	163.9±37.4	164.7±43.6	224.3±32.0	0.000	0.000	0.876
HDL (mg/dl)	48.8±15.1	48.3±14.0	74.8±27.2	0.000	0.000	0.867
LDL (mg/dl)	107.8±32.5	102.7±29.5	135.2±43.8	0.032	0.004	0.415
ApoB (μg/μl)	4.2±3.1	7.7±13.1	1.9±1.3	0.022	0.167	0.004
ApoE (μg/μl)	0.113±0.080	0.214±0.171	0.058±0.016	0.032	0.000	0.000

AFP, α-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transferase; BUN, TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; ApoB, apolipoprotein B; ApoE, apolipoprotein E.
[a] comparison between HBV patients and normal controls
[b] comparison between HCV patients and normal controls
[c] comparison between HBV and HCV patients

Table 3. Comparison of apolipoprotein E genotype between HBV and HCV patients

n (%)

Hepatitis virus	Apolipoprotein E genotype						Total
	ε2/ε2	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4	ε4/ε4	
HBV	0 (0)	15 (13.0)	4 (3.5)	83 (72.2)	13 (11.3)	0 (0)	115 (100)
HCV	0 (0)	13 (10.2)	1 (0.8)	101 (78.9)	13 (10.2)	0 (0)	128 (100)

Table 4. Comparison of apolipoprotein E gene allele between HBV and HCV patients

n (%)

Hepatitis virus	ApoE allele			Total (%)
	ε2	ε3	ε4	
HBV	19 (8.3)	194 (84.3)	17 (7.4)	230 (100)
HCV	14 (5.5)	228 (89.1)	14 (5.5)	256 (100)

ε3/ε3 group. ApoE levels were similar in HBV and HCV patients without the apoE genotype (Table 5).

DISCUSSION

The male ratio of HBV patients in this study was very high, unlike the HCV patients. In addition, the HBV patients were younger than the HCV patients in Korea. Regarding

Table 5. Comparison of hematological characteristics between HBV and HCV patients by apoE genotype

Characteristics	Hepatitis virus	ε2/ε3	ε2/ε4	ε3/ε3	ε3/ε4
n	HBV	15	4	83	13
	HCV	13	1	101	13
AFP (ng/ml)	HBV	65.6±83.5	3.5±1.4	95.3±572.0	4.6±4.4
	HCV	76.6±197.3	3.8	73.3±444.9	124.4±305.1
Total protein (g/dl)	HBV	7.3±1.0	7.0±0.5	7.3±0.9	7.0±0.8
	HCV	7.5±0.9	6.7	7.4±0.7	7.3±0.8
Albumin (g/dl)	HBV	3.9±0.6	4.1±0.2	4.0±0.6	4.1±0.5
	HCV	4.0±0.7	3.8	4.0±0.6	3.9±0.5
AST (IU/l)	HBV	71.9±143.6	19.8±5.7	55.0±67.1	43.2±50.6
	HCV	62.5±40.6	19.0	61.2±70.8	44.7±41.2
ALT (IU/l)	HBV	66.9±148.3	21.8±6.1	45.3±50.2	29.4±22.4
	HCV	55.8±50.5	33.0	50.3±54.7	29.7±15.4
Total bilirubin (mg/dl)	HBV	2.1±8.2	0.8±0.1	1.2±2.2	2.9±5.9
	HCV	0.9±0.4	1.0	1.1±1.8	1.0±0.6
ALP (IU/l)	HBV	293.1±148.3	218.5±27.6	312.9±259.1	211.5±86.5
	HCV	302.3±146.4	188.0	304.7±234.8	301.1±126.2
γ-GTP (IU/l)	HBV	72.6±71.6	31.0±2.8	86.3±148.0	30.2±16.2
	HCV	93.8±81.2	23.0	67.6±97.2	53.3±288.5
BUN (mg/dl)	HBV	21.5±11.5	14.5±1.8	18.1±11.1	15.7±10.7
	HCV	23.5±28.3	17.6	18.8±12.3	20.3±15.8
Creatinine (mg/dl)	HBV	1.2±0.8	1.1±0.2	1.3±1.5	1.1±0.2
	HCV	1.2±0.6	0.9	1.3±1.1	1.7±2.4
Total cholesterol (mg/dl)	HBV	157.0±43.7	156.0±6.4	166.0±43.6	161.9±34.8
	HCV	155.8±28.6	214.0	165.8±46.5	161.1±32.3
TG (mg/dl)	HBV	128.1±90.0	75.0±22.6	119.4±84.5	103.0±43.8
	HCV	116.8±70.2	92.0	125.9±96.0	106.1±40.8
HDL (mg/dl)	HBV	45.8±14.6	35.0	48.3±15.0	51.4±19.5
	HCV	44.3±12.6	—	48.1±14.8	54.3±6.5
LDL (mg/dl)	HBV	95.1±40.2	85.0	105.7±32.8	105.7±13.1
	HCV	88.4±36.3	—	104.0±29.7	110.6±12.6
ApoB (μg/μl)	HBV	4.822±4.0	3.290±1.9	6.452±11.0	3.622±1.9
	HCV	5.182±6.6	1.627±0.004	8.244±14.4	6.715±6.7
ApoE (μg/μl)	HBV	0.177±0.094	0.066	0.174±0.152	0.063±0.040
	HCV	0.200±0.119	0.126	0.222±0.179	0.179±0.155

AFP, α-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, phopho; γ-GTP, γ-glutamyl transferase; BUN, TG, triglyceride; HDL, high density lipo; LDL, low density; ApoB, apolipoprotein B; ApoE, apolipoprotein E.

latency period, the prevalence rates of chronic HBV and HCV were higher in middle-aged patients. Increasing awareness regarding blood infection led to the prohibition of the reuse of medical materials such as needles and syringes in Korea in the 1980s. As a result of this policy, it is anticipated that the rate of infected persons will decline. The policy is followed much more effectively in the HCV risk group, although the reason is unclear. Studies from a public health perspective are needed.

In this study, we found that HBV and HCV infection are strongly associated with low levels of total cholesterol. In addition, apoB and apoE levels were higher in both HBV and HCV patients than in healthy controls. HBV and HCV both affect lipid metabolism in the liver; HCV has more of an effect than HBV due to high levels of TG, apoB, and apoE. This research demonstrates the hypothesis of a prior *in vitro* study showing that apoB and apoE enrich the HCV virion, especially apoE (9).

Many studies have investigated the relationship between HCV and cholesterol. Cholesterol has two metabolism pathways: endogenesis and exogenesis. In the endogenesis pathway, hepatocytes synthesize cholesterol through the mevalonate pathway. At this time, we anticipate that HCV uses geranylgeranyl pyrophosphate, which is a substrate in the mevalonate pathway, for replication. HCV interrupts cholesterol synthesis, and therefore, induces cholesterolemia. Because total cholesterol in HCV patients are lower than normal group in this study.

In the exogenesis pathway, cholesterol is transported from the intestine to the liver with lipoproteins, including very low density lipoproteins (VLDL), low density lipoproteins (LDL), and apolipoproteins. Then, cholesterol is regenerated to VLDL and release into the bloodstream. At this time, we anticipate that apoE mediates the entry of HCV from the blood to the hepatocytes, forming a lipo-viral particle (LVP), and releases from the hepatocytes into the blood via. Because apoE in HCV patients are lower than normal group in this study (9~18).

In this study, the HCV patients had a high distribution of ε3/ε3 almost 80%. Heterotypes such as ε2/ε3, ε2/ε4, and ε3/ε4 were more common in the HBV patients. In South Korea, the ε3/ε3 genotype distribution is about 75% in normal people. Therefore, ε3/ε3 is more common in HBV and HCV patients, particularly HCV. In addition, the distributions of the ε2/ε3 and ε3/ε4 genotypes are about 5~7% and 13~16%, respectively, in normal people. Distribution of ε2/ε3 is more common than ε3/ε4 (19, 20).

The apoE ε2 allele is associated with low affinity to the LDL receptor and the apoE ε4 allele is associated with downregulation of the LDL receptor. Therefore, we anticipate that the apoE ε3 allele is the most common type in HCV and HBV, especially HCV.

A study conducted in China demonstrated an association between HBV infection and the apoE ε2 allele. That result is similar to the finding in this study that ε2/ε3 is more common in HBV patients (21). A similar study was conducted in the UK, and an association between HCV infection and the apoE ε3 allele was demonstrated (22) Thus, we anticipate that there is no association by race between HCV infection and the apoE ε3 allele.

In another study, the apoE ε4 allele was shown to be associated with mild liver disease. Therefore, the researchers anticipated that the apoE ε4 allele protects from severe liver disease (23). Similarly, the apoE ε4 allele was less prevalent in this study, especially in the HCV patients.

The ε2/ε3 and ε3/ε3 genotype groups presented representative levels of HBV and HCV characteristics in serum. We anticipate that among heterotypes with the apoE ε3 allele, the apoE ε2 allele will have no effect on HBV and HCV infection, because HBV and HCV induce only a transcription of the apoE ε3 allele.

In this study, we compared differences in hematological characteristics in the sera of HBV and HCV patients and sought to find a key biomarker to differentiate between HBV and HCV infection. We found that both HBV and HCV infections have strong associations with low levels of total cholesterol, apoB, and apoE, particularly HCV. As a result of apoE genotyping, we demonstrated an association with HCV infection and the apoE ε3 allele. Moreover, heterotypes such as ε2/ε3, ε2/ε4, and ε3/ε4 are more common in HBV patients. We confirmed the relationship of HBV and HCV in lipid metabolism. Analyses with larger samples and greater

diversity of region are needed in order to contribute to the early treatment of high risk groups and the development of HCV and HBV diagnosis standards and medicine.

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