Clin. Lab. 2019;65:XXX-XXX

ORIGINAL ARTICLE

Serum Lipid Metabolic Derangement is Associated with Disease Progression During Chronic HBV Infection

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SUMMARY

Background: **To investigate the relationship between serum lipid levels and disease progression during chronic hepatitis B virus infection.**
Methods: **We selected 73 healthy controls and 163 patients with chronic HBV infection as the study subjects. The chronic HBV infection patients were divided into the HBV carrier group (74 patients), chronic hepatitis B group (71 patients), and liver cirrhosis group (21 patients). The age, gender, body mass index, blood lipid index, liver function index, and HBV DNA levels of all participants were tested and recorded. A *t*-test or the Mann-Whitney *U* test was used to compare the data between two groups; data from multiple groups were compared using one-way ANOVA or the Kruskal-Wallis Test.**
Results: **We observed that the serum HDL cholesterol (1.00 ± 0.30 mmol/L in the HBV-infected group, 1.29 ± 0.23 mmol/L in the control group) and APOA (1.29 ± 0.35 mmol/L, 1.36 ± 0.21 mmol/L, respectively) concentrations were significantly lower in the HBV-infected group than in the control group ($p < 0.05$). As the disease progressed, the blood lipid and lipoprotein values were significantly lower in the cirrhosis group TC (3.26 ± 1.00 mmol/L), HDL cholesterol (0.77 ± 0.33 mmol/L), LDL cholesterol (2.09 ± 0.62 mmol/L), and APOB (0.57 ± 0.18 mmol/L) compared with the control group, the carrier group, and the chronic hepatitis B group ($p < 0.05$). The serum HBV DNA level was significantly, positively correlated with the blood HDL concentration (carrier group $R = 0.340$, $p = 0.02$; chronic hepatitis B group $R = 0.329$, $p = 0.014$). There was no correlation between the HBV DNA and lipid levels in patients with cirrhosis.**
Conclusions: **Serum lipid metabolic derangement was associated with disease progression during chronic HBV infection. Liver function and blood lipid levels were significantly lower in patients with hepatitis B-related cirrhosis.**
(Clin. Lab. 2019;65:xx-xx. DOI: 10.7754/Clin.Lab.2019.190525)

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Manuscript accepted June 4, 2019

KEY WORDS

hepatitis B virus infection, lipid, total cholesterol (TC), high density lipoprotein (HDL), HBV DNA, cirrhotic

INTRODUCTION

Hepatitis B virus (HBV), a small, circular, double-stranded, liver-tropic DNA virus that can cause acute and chronic hepatitis in humans, continues to be a worldwide public health problem. Liver disease caused by chronic hepatitis B is the main cause of death related

to HBV infection; 2 billion people are estimated to be infected, and more than 350 million people are chronic carriers of the virus [1]. The continuous replication of hepatitis B virus, which contributes to disease progression, is a major risk factor for liver fibrosis, cirrhosis, and hepatocellular carcinoma [2-4]. Ress et al. [5] reported that chronic hepatitis C can directly interfere with serum lipid metabolism by altering liver function, while the low level of triglyceride content in the VLDL particles of HCV-infected patients further demonstrate that the virus may directly affect VLDL secretion [6]. In recent years, however, dyslipidemia has been widely studied in patients with chronic hepatitis B. The liver, as an organ that maintains homeostasis in the body, participates in lipid synthesis and catabolism [7] and plays an important role in regulating the internal and external circulation of lipid metabolism.

Metabolic abnormalities are common in chronic hepatitis B virus infections. Previous studies [8,9] have shown that changes in serum lipid levels in patients with chronic hepatitis B, hepatitis B virus-associated cirrhosis or hepatocellular carcinoma, which suggests that HBV infection can alter lipid metabolism in the host. *In vitro* studies have shown that an adenovirus containing the HBV genome can affect cholesterol metabolism by upregulating the expression of related genes in hepG2 cells [10]. The long-term surge in proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and interferon-α (IFN-α), is related to dyslipidemia during chronic HBV infection [11]. Furthermore, lipoproteins, as important components of lipids in the blood, are involved in lipid transport and metabolism. It would be very helpful to the clinical treatment and prognosis of chronic HBV infection if we can further clarify the relationship between lipoproteins and chronic HBV infection. Thus, we measured serum TC, TG, HDL, LDL, APOA, and APOB concentrations and serum ALT, AST, and HBV DNA levels to analyze the correlation between plasma lipids and disease progression during chronic HBV infection.

MATERIALS AND METHODS

Patient population

We enrolled 165 patients with chronic hepatitis B virus infection in this study, 73 of whom were diagnosed as HBV carriers and were enrolled in the Hepatitis B virus Carrier Group (ASC group); 72 of whom were diagnosed as chronic hepatitis B patients, did not receive antiviral therapy, and were enrolled in the chronic hepatitis B group (CHB group); and 21 of whom were diagnosed with hepatitis B virus-related cirrhosis, did not receive antiviral therapy, and were enrolled as the cirrhosis group (LC group). All patients were diagnosed in the outpatient department of hepatology at the Second Affiliated Hospital of Anhui Medical University between March 2017 and August 2017. All cases were diagnosed in accordance with the naming and diagnostic criteria of the guidelines for the prevention and treatment of chronic hepatitis B revised by the hepatology association and infectious diseases branch of the Chinese Medical Association in 2015 [12]. Patients with other types of hepatitis, coinfection with other viruses, decompensated liver cirrhosis, hepatocellular carcinoma, drug-induced liver disease, autoimmune liver disease, metabolic liver disease, habitual alcoholism, diabetes, or treated dyslipidemia were excluded from this study. The 73 people in the control group were all healthy persons. This retrospective study was approved by the Ethics Committee of Anhui Medical University. This study was approved by the ethics Committee before it was launched (No. 2012102). All participants provided informed consent prior to specimen collection. The study was carried out in accordance with the Helsinki Declaration of 1975. After 12 hours of fasting, 10 mL of peripheral blood was taken, and the 10 mL intravenous blood drawn from the subjects was allowed to clot in sterile non-heparinized vacutainers and centrifuged at 3,000 r/min for 10 minutes. The serum was collected into new vials and stored at -80°C until use.

Demographic data and basic laboratory tests

Demographic data, including age, gender, and body mass index (BMI), were collected from each patient's medical records. Clinical and laboratory results were also collected from the medical records. Laboratory variables analyzed included hepatitis B virus DNA (HBV-DNA) levels, aspartate aminotransferase (AST) levels, and alanine aminotransferase (ALT) levels. HBV DNA levels were determined by PCR using the fluorescent probe method (hepatitis B virus nucleic acid detection kit, instrument model: Agilent Mx3000P). An HBV DNA assay value higher than 500 IU/mL was considered positive; otherwise, the test was considered negative.

Liver function tests: The alanine aminotransferase (ALT) concentration in the sample was detected using an alanine aminotransferase assay kit (colorimetric method). The aspartate aminotransferase (AST) concentration in that sample was detected using an aspartate aminotransferase assay kit (enzymatic method). They were both detected by a fully automated biochemical analyzer (instrument model: RML-MAX-RMS).

Serum lipid profiles

The lipid and lipoprotein markers tested included the levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A (APOA), and apolipoprotein B (APOB), which were detected by a BECKMAN AU 5800 instrument in the clinical laboratory of the Second Hospital of Anhui Medical University.

Blood lipid levels detection: The concentrations of total cholesterol (TC) and triglycerides (TG) in the sample to be tested were detected by a cholesterol determination kit (endpoint method) and triglyceride determination kit (GPO - PAP method), respectively. A high-density lipo-

protein cholesterol assay kit (direct method - selective inhibition method) and a low-density lipoprotein assay kit (enzymatic method) were used to detect the concentrations of high-density lipoprotein (HDL) and low-density lipoprotein (LDL). The concentrations of apolipoprotein A (APOA) and apolipoprotein B (APOB) in the sample were detected using an apolipoprotein A assay kit (immunoturbidimetry) and an apolipoprotein B assay kit (immunoturbidimetry), respectively.

Statistical analysis

When comparing the differences between two groups with Gaussian data distributions, we conducted an independent sample *t*-test. When the data did not follow a Gaussian distribution, the non-parametric Mann-Whitney *U*-test was used. For the analysis of multiple datasets that were all Gaussian distributions, the variance of the sample data was analyzed by one-way analysis of variance and an LSD-*t*-test. Otherwise, Dunnett's T3 test was used. When the data did not follow a Gaussian distribution, the Kruskal-Wallis test, a non-parametric test, was used. For the correlation analysis, Pearson's analysis method was used for data with a Gaussian distribution; otherwise, Spearman's analysis was used. Counting data are expressed in percentage (%) and chi-square test is used.

All statistical analyses were performed using SPSS 17.0 statistics software. A two-tailed $p < 0.05$ was considered significant. Quantitative data are expressed as the mean and standard deviation (x s). GraphPad Prism 5 software was used to generate all images.

RESULTS

Differences in serum lipid levels between chronic HBV infection patients and healthy controls

As shown in Table 1, 167 patients with HBV infection, including HBV carriers, patients with chronic hepatitis B, and patients with cirrhosis, were enrolled in the HBV infection group. Table 1 summarizes the clinical characteristics of the healthy controls and chronic HBV infection groups. The mean age of the control group was 35.0 ± 12.10 years, which was not significantly different from that of the chronic HBV infection group ($p > 0.05$). The gender ratio difference between the two groups was not significant. There were no significant differences in other demographic data, including BMI ($p > 0.05$). In routine laboratory tests, the AST and ALT levels in HBV-infected patients were significantly higher than those in the control group.

As shown in Table 2, compared with those in the healthy control group (TC 4.48 mmol/L, TG 1.10 mmol/L, HDL 1.29 mmol/L, LDL 2.63 mmol/L, APOA 1.36 mmol/L, APOB 0.75 mmol/L), the levels of the serum lipids and lipoproteins measured in the HBV-infected patients (TC 4.29 mmol/L, TG 1.05 mmol/L, HDL 1.00 mmol/L, LDL 2.60 mmol/L, APOA 1.29 mmol/L, APOB 0.72 mmol/L) tended to decrease; however, only the differences in HDL ($p = 0.000$) and APOA ($p = 0.026$) were statistically significant (Table 1, Figure 1). The Mann-Whitney *U*-test was used to determine whether alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were different between the control group and HBV-infected group. The Mann-Whitney *U*-test results showed that the difference between the control group ALT level (average rank = 39.83) and the HBV infection group ALT level (average rank = 128.13.48) was statistically significant ($u = 716.50$, $z = -8.840$, $p = 0.000$). The difference in the AST level between the control group (average rank = 66.18) and HBV infection group (average rank = 120.10) was statistically significant ($u = 2{,}034.00$, $z = -5.394$, $p = 0.000$) (Table 2, Figure 1).

Associations between blood lipid levels and the progression of HBV infection

We summarized the clinical characteristics of the healthy controls and different stages of chronic HBV infection in Table 3. The mean age of the control group was 35.0 ± 12.10 years old. There was no significant difference between the ages of the different groups ($p > 0.05$). There was no significant difference in the gender ratio between the control groups and HBV-infected groups. Other demographic indicators, such as BMI, were not significantly different ($p > 0.05$) (Table 3).

By one-way analysis of variance, the sera of the healthy control group, hepatitis B carrier group, chronic hepatitis B group, and liver cirrhosis group were compared. There was no difference in the triglyceride levels of the groups ($p = 0.634$), but other indicators differed significantly between the healthy control group (control), hepatitis B carrier group (ASC), chronic hepatitis B group (CHB), and cirrhosis group (LC) groups ($p < 0.05$). In addition, the TC and HDL levels were significantly higher in the healthy control group than in the other three groups (Table 4).

Correlations between the viral load and blood lipid levels

Based on the HBV-DNA level determination, we divided the HBV carrier group into a DNA-positive group and DNA-negative group. As shown in Table 5, the basic data of the two groups, including gender, age, and BMI values, were not significantly different ($p > 0.05$). The liver function parameters, alanine aminotransferase (ALT) (54.59 IU/L) and aspartate aminotransferase (32.86 IU/L) levels, were higher in the DNA-positive group than in the DNA-negative group (32.71 IU/L, 23.18 IU/L). The DNA-positive group TC (4.14 mmol/L), TG (1.02 mmol/L), HDL (0.99 mmol/L), LDL (2.51 mmol/L), and APOB (0.70 mmol/L) levels were significantly lower than those of the DNA-negative group ($p < 0.05$), but the positive group had a higher APOA level (1.54 mmol/L) than the negative group ($p < 0.05$). A correlation analysis was carried out with the HBV DNA and blood lipid levels after logarithmic conversion. The results are shown in Table 6 and Figure

Table 1. Clinical and laboratory features of all the hepatitis B patients.

Parameter	Control	HBV infection	*t*-test/χ^2-test
	(n = 73)	(n = 167)	p-value
Mean age (years)	35.33 ± 12.10 [a]	36.74 ± 10.53 [a]	p > 0.05
BMI (kg/m^2)	21.80 ± 2.84 [a]	22.93 ± 0.31 [a]	p > 0.05
Gender (male%)	71%	73%	p > 0.05

HBV - hepatitis B virus, BMI - body mass index, a - Gaussian distribution.

Table 2. Indicators of blood lipid levels and liver function in the healthy control group and HBV patient group.

Presenting clinical signs	Control (n = 73)	HBV infection (n = 167)	*t*-test/Mann-Whitney *U*-test	
			T value/Z value	p-value
ALT	39.83 [b]	128.13 [b]	-8.840	0.000
AST	66.18 [b]	120.10 [b]	-5.394	0.000
TC (mmol/L)	4.48 ± 0.68 [a]	4.29 ± 0.95 [a]	1.825	0.070
TG (mmol/L)	1.10 ± 0.44 [a]	1.05 ± 0.37 [a]	0.825	0.410
HDL (mmol/L)	1.29 ± 0.23 [a]	1.00 ± 0.30 [a]	7.279	0.000
LDL (mmol/L)	2.63 ± 0.36 [a]	2.60 ± 0.61 [a]	0.464	0.643
APOA (mmol/L)	1.36 ± 0.21 [a]	1.29 ± 0.35 [a]	2.245	0.026
APOB (mmol/L)	0.75 ± 0.20 [a]	0.72 ± 0.20 [a]	0.979	0.328

HBV - hepatitis B virus, AST - aspartate 2-oxoglutarate aminotransferase, ALT - alanine 2-oxoglutarate aminotransferase, TC - total cholesterol, TG - triglycerides, HDL - nigh-density lipoprotein, LDL - low-density lipoprotein, APOA - apolipoprotein A, APOB - apolipoprotein B, [a] - Gaussian distribution, [b] - mean rank.

Table 3. Basic data of the normal control group and HBV progression groups.

Parameter	Control	ASC	CHB	LC	*t*-test/χ^2-test
	(n = 73)	(n = 74)	(n = 72)	(n = 21)	p-value
Mean age (years)	35.33 ± 12.10 [a]	35.15 ± 16.03 [a]	37.41 ± 19.37 [a]	40.14 ± 19.65 [a]	p > 0.05
BMI (kg/m^2)	21.80 ± 2.84 [a]	23.41 ± 3.11 [a]	22.97 ± 2.99 [a]	21.16 ± 2.77 [a]	p > 0.05
Gender male%	71.23%	68.91%	73.61%	76.19%	p > 0.05

ASC - hepatitis B virus carriers, CHB - chronic hepatitis B patients, LC - liver cirrhosis patients, BMI - body mass index, [a] - Gaussian distribution.

3. The serum viral load was positively correlated with the CHO, HDL, and LDL levels in the carrier group, with r values of 0.312, 0.340, and 0.346, respectively; the difference was statistically significant ($p < 0.05$). The serum HDL level and the HBV DNA levels in chronic hepatitis B patients had a correlation coefficient $r = 0.329$ ($p < 0.05$). In the liver cirrhosis group, no significant correlation was found between the lipid profile and the viral load.

DISCUSSION

The analysis of patient samples from the four study groups shows that the effects of different stages of HBV infection on the blood lipid and lipoprotein levels are of interest. Generally, most disease conditions affecting the distribution of the host's serum will affect serum total cholesterol levels. The changes in the serum lipid levels in patients with HBV infection progression (Table 4) suggest that the total cholesterol and high-density lipo-

Table 4. Changes in serum lipid levels and liver function in normal control patients and HBV infection progression patients.

Presenting clinical signs	Control	ASC	CHB	LC	Kruskal-Wallis test	ANOVA	
	(n = 73)	(n = 74)	(n = 72)	(n = 21)	P^1	P^2	P^3
ALT (IU/L)	39.83 [b]	111.50 [b]	150.22 [b]	112.35 [b]	0.000	-	-
AST (IU/L)	66.18 [b]	88.98 [b]	143.59 [b]	153.00 [b]	0.000	-	-
Lg (HBV DNA)	-	5.41 ± 2.11 [a]	5.39 ± 1.74 [a]	3.80 ± 1.54 [a]	-	0.001	0.031
TC (mmol/L)	4.48 ± 0.68 [a f]	4.39 ± 0.79 [a f]	4.48 ± 0.91 [a f]	3.26 ± 1.00 [a c d e]	-	0.099	0.000
TG (mmol/L)	1.10 ± 0.44 [a]	1.07 ± 0.41 [a]	1.13 ± 0.42 [a]	1.00 ± 0.42 [a]	-	0.953	0.610
HDL (mmol/L)	1.29 ± 0.23 [a d e f]	1.03 ± 0.27 [a c f]	1.04 ± 0.30 [a c d]	0.77 ± 0.33 [a c d e]	-	0.170	0.000
LDL (mmol/L)	2.63 ± 0.36 [a f]	2.67 ± 0.54 [a f]	2.67 ± 0.61 [a f]	2.09 ± 0.62 [a c d e]	-	0.005	0.000
APOA (mmol/L)	1.36 ± 0.21 [a e]	1.42 ± 0.30 [a e]	1.17 ± 0.29 [a c d]	1.16 ± 0.51 [a]	-	0.000	0.000
APOB (mmol/L)	0.75 ± 0.20 [a f]	0.74 ± 0.16 [a f]	0.74 ± 0.20 [a f]	0.57 ± 0.18 [a c d e]	-	0.121	0.001

[a] - Gaussian distribution, [b] - mean rank, [c] - $p < 0.01$ vs. control, [d] - $p < 0.01$ vs. ASC, [e] - $p < 0.01$ vs. CHB, [f] - $p < 0.01$ vs. LC, HBV - hepatitis B virus, AST - aspartate 2-oxoglutarate aminotransferase, ALT - alanine 2-oxoglutarate aminotransferase, TC - total cholesterol, TG - triglycerides, HDL - high-density lipoprotein, LDL - low-density lipoprotein, APOA - apolipoprotein A, APOB - apolipoprotein B, P^1 - p-value of the Kruskal-Wallis Test, P^2 - p-value of the homogeneity test of variance, P^3 - difference between groups in variance analysis, Lg (HBV DNA) - pair values of HBV DNA measurements.

Table 5. Comparing the difference in each index between the DNA-positive group and the DNA-negative group of hepatitis B virus carriers.

Presenting clinical signs	ASC		
	DNA(+) (n = 49)	DNA(-) (n = 25)	*t*-test/χ^2-test
Mean age (years)	35.10 ± 9.82 [a]	35.24 ± 11.30 [a]	p > 0.05
Gender male%	69.38%	68.00%	p > 0.05
BMI (kg/m^2)	22.91 ± 2.80 [a]	24.28 ± 3.44 [a]	p > 0.05
ALT (IU/L)	54.59 ± 26.90 [a]	32.71 ± 13.53 [a]	p < 0.05
AST (IU/L)	32.86 ± 19.33 [a]	23.18 ± 7.74 [a]	p < 0.05
TC (mmol/L)	4.14 ± 0.72 [a]	4.73 ± 0.77 [a]	p < 0.05
TG (mmol/L)	1.02 ± 0.41 [a]	1.20 ± 0.59 [a]	p < 0.05
HDL (mmol/L)	0.99 ± 0.29 [a]	1.10 ± 0.23 [a]	p < 0.05
LDL (mmol/L)	2.51 ± 0.45 [a]	2.86 ± 0.61 [a]	p < 0.05
APOA (mmol/L)	1.54 ± 0.31 [a]	1.26 ± 0.21 [a]	p < 0.05
APOB (mmol/L)	0.70 ± 0.14 [a]	0.81 ± 0.19 [a]	p < 0.05

ASC - hepatitis B virus carriers, AST - aspartate 2-oxoglutarate aminotransferase, ALT - alanine 2-oxoglutarate aminotransferase, TC - total cholesterol, TG - triglycerides, HDL - high-density lipoprotein, LDL - low-density lipoprotein, APOA - apolipoprotein A, APOB - apolipoprotein B, [a]:- Gaussian distribution, BMI - body mass index.

protein levels decrease gradually with the progression of HBV infection.

As previously reported [13], cholesterol levels are affected by chronic viral hepatitis and disease severity. The interaction between the serum total cholesterol level and HBV in the cells of patients with HBV infection is involved in virus fusion, target cell infection, and hepatocyte degeneration and necrosis, which aggravate liver function damage and affect the formation, esterification and emptying of cholesterol [14], ultimately leading to a reduction in the serum cholesterol level.

In this study, unlike previous studies [15], there was no significant difference in the total cholesterol level between the two groups, which may be related to demo-

Table 6. Correlation test between HBV DNA and serum lipid levels.

HBV DNA	TC	TG	HDL	LDL	APOA	APOB
	r	r	r	r	r	r
ASC	0.312 [g]	-0.064	0.340 [g]	0.346 [f]	-0.135	0.098
CHB	0.127	-0.215	0.329 [g]	0.146	0.157	-0.007
LC	0.317	0.233	0.267	0.282	0.414	0.289

ASC - hepatitis B virus carriers, AST - aspartate 2-oxoglutarate aminotransferase, ALT - alanine 2-oxoglutarate aminotransferase, TC - total cholesterol, TG - triglycerides, HDL - high-density lipoprotein, LDL - low-density lipoprotein, APOA - apolipoprotein A, APOB - apolipoprotein B, [g] - $p < 0.05$.

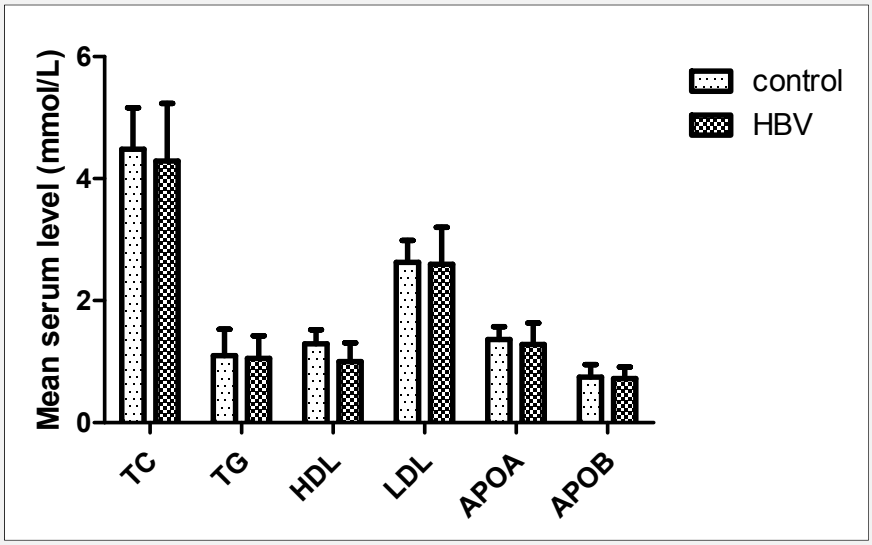

Figure 1. Comparison of the serum lipid and lipoprotein concentrations between the healthy control group and the chronic HBV infection group.

The p-values for the TC, TG, HDL, LDL, APOA, and APOB levels were 0.00, 0.410, 0.000, 0.643, 0.026, and 0.328, respectively.

graphic differences. In addition, different genotypes and ethnic differences may also be the cause of this different result.

The liver is the main organ involved in blood lipid metabolism [7]. With the decline in liver function associated with HBV infection, many physiological indicators in patients with chronic hepatitis B will be abnormal [15]. It is worth noting that, as shown in Table 4, the liver function indexes, glutamic pyruvic transaminase (ALT) and glutamic oxaloacetic transaminase (AST), in the liver cirrhosis group are significantly increased, suggesting that liver damage aggravates disease progression; the blood lipid and apolipoprotein levels in the liver cirrhosis group were significantly lower than those of the other three groups, suggesting that liver damage may be related to the decreases in the blood lipid and lipoprotein levels. Subsequent studies of the HBV DNA levels showed no significant correlations between the viral load and the levels of blood lipids and apolipoproteins in cirrhosis patients.

A significant reduction in the blood lipid levels in cirrhotic patients compared to those of the control group has been demonstrated in other studies to be attributable to an impairment in liver function. Cirrhosis is a complex pathological process. Hepatic fibrosis and the formation of false lobules are typical manifestations of cirrhosis under the microscope, and hepatic fibrosis is the early pathological change in the liver in patients with

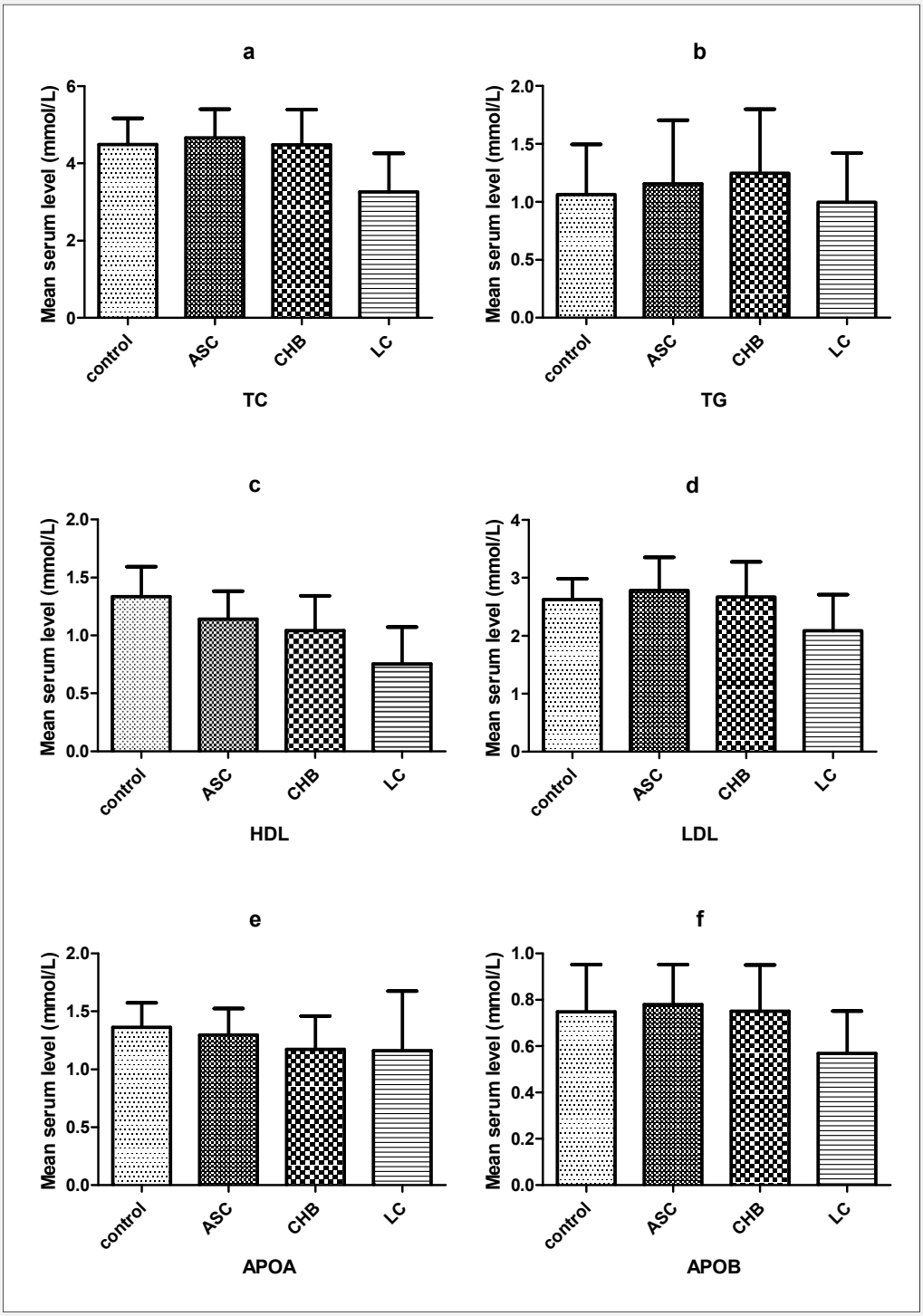

Figure 2. Changes in the serum lipid levels in the HBV progression and healthy control groups.

The serum lipid and lipoprotein levels (TC, HDL, LDL, and APOB) in the cirrhosis group were significantly lower than those in the other three groups ($p < 0.05$).
There were no significant differences in the TG levels between the four groups, and there was a significant difference in the levels of APOA between the chronic hepatitis B group and the control group and the carrier group ($p < 0.05$).

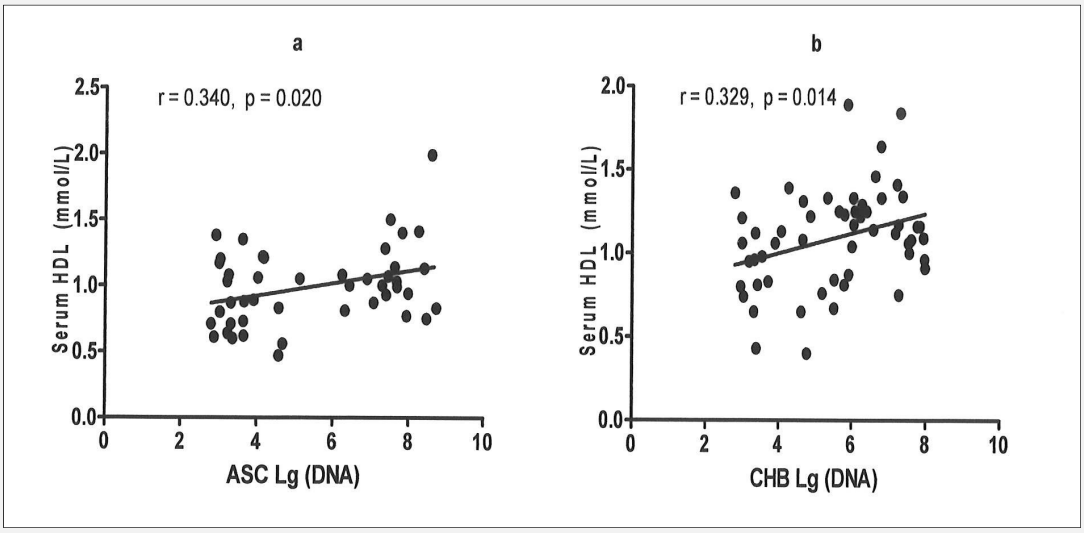

Figure 3. Correlation test between the HDL levels and viral load in the DNA-positive groups.

a: Correlation between serum HDL levels and viral load in the HBV carrier group DNA-positive patients, correlation coefficient r = 0.340, p = 0.02; b: Correlation between the serum HDL levels and DNA load in patients with chronic hepatitis B, r = 0.329, p = 0.014.

chronic hepatitis B; the continuous development of hepatic fibrosis will destroy the normal structure of the liver, further affect the normal function of the liver, and ultimately lead to pathological and physiological damage to the liver [16]. These effects are mentioned in the results of many scholars. For example, in studies by Cristin, Constantin and others [17-19], it was found that the changes in lipid metabolism in viral hepatitis cirrhosis may be associated with the histological changes in hepatocytes that result in changes in liver function. Arain [11] also showed that circulating blood lipid levels decreased in patients with hepatitis B-related cirrhosis as liver function impairment worsened. Moreover, similar results were obtained in a 2017 blood lipid profile survey of patients with hepatitis B cirrhosis. In addition, hepatitis B virus replication is the key to liver injury and liver cirrhosis progression [20], and virus DNA removal to a large extent (more than 90%) relies on antiviral cytokines, which are produced by responding immune cells [21]. However, in the process of virus removal, cytotoxic T cells recruit a large number of inflammatory cells into the liver, leading to the initiation of necrotizing inflammatory reactions by the immune response [22]. Severe effects on liver function [23] and lipid metabolism have also been noted. In addition, in regard to the physiological function of the liver, when liver cirrhosis occurs, glucose metabolism disorders, which affect liver glycogen and sugar and increases fat mobilization, will lead to reduced blood lipid synthesis and decomposition.

However, the mechanism of interaction between liver cirrhosis and lipid metabolism is complex, and the mechanism reducing lipid and lipoprotein levels has not been elucidated in detail and needs further study.

In addition, it is shown in Table 2 that HDL measurements are lower in HBV patients than in normal controls, similar findings are shown in Table 4, and HDL levels are gradually reduced as HBV infection progresses. In Table 6, HDL levels were also significantly lower in the DNA-positive group than in the DNA-negative group. These results suggest that HDL levels are closely related to HBV infection.

It is well-known that chronic hepatitis B has long been defined as a chronic inflammatory disease, that liver cells are the target cells of HBV infection, and that HBV infection can lead to hepatocyte injury and impair the integrity of hepatocyte function. As mentioned earlier [16], the liver is also the main site for synthesizing and metabolizing blood lipids; thus, HBV infection would affect HDL synthesis, transport and decomposition and ultimately lead to a decreased HDL concentration in the peripheral blood. HDL is part of innate immunity, and in addition to its ability to reverse cholesterol transport (RCT), HDL has endothelial protective, antioxidant, anti-inflammatory, and antithrombotic properties [24]. HBV infection results in hepatocyte injury; impaired functional integrity in hepatocytes; effects on HDL synthesis, transport and decomposition; and ultimately a reduction in the HDL concentration in the peripheral circulation [25].

Interestingly, in this study, there was a significant positive correlation between serum HDL and viral DNA levels in HBV carriers and patients with chronic hepatitis B (carrier group: r = 0.340, p = 0.02; CHB group: r = 0.329, p = 0.014). This observation is remarkably inconsistent with previous reports [26,27].

However, Stephen Zewinger et al. [28] studied patients with high serum amyloid A (SAA) levels and found that high HDL-C was associated not only with increased cardiovascular mortality but also with increased all-cause mortality, suggesting that SAA accumulation may change and damage the biological effect of HDL by reversing the vascular protection function of HDL. Although SAA is an acute phase protein, it is currently only reported that it may be a constituent of HDL particles in CAD and CKD diseases, specifically, changes in the composition of HDL particles have been shown to be closely related to decreases in the anti-inflammatory activity of HDL [29,30]. Furthermore, *in vitro* experiments also provide supporting evidence for this; mouse tyrosine free radical oxidation with HDL and oxidation/nitration with HDL showed opposite effects [31,32], showing that HDL has a role in promoting lipid oxidation and that the oxidation of a lipid is itself proinflammatory [33].

Most of the serum HDL measured by us was produced by the liver and intestines, which did not indicate the biological function of HDL [30]. In this experiment, the HDL levels were positively correlated with the HBV carriers and HBV patients' serum viral load. Combined with the results in Table 4, the serum viral load in patients with liver cirrhosis was significantly reduced compared with carrier and chronic HBV patients' serum viral loads. At the same time, the serum lipid level was also significantly reduced in each group, which may be a manifestation of the anti-inflammatory and antioxidant effects of HDL.

CONCLUSION

In summary, blood lipid monitoring, especially monitoring for the hypolipidemia observed in HBV-cirrhosis patients, may help to identify the diagnosis of HBV infection and the different stages of HBV infection in China. There is no obvious positive correlation between the blood lipid levels and viral load, which may be due to the severe damage to liver cell function that changes blood lipid metabolism. These observations have important guiding significance for early detection, early treatment, and treatment in different stages of HBV infection. In addition, the positive correlation between the serum HDL levels and HBV DNA levels in patients with non-end-stage HBV infection may also provide evidence for the proinflammatory and pro-oxidative effects of HDL [31,32].

Acknowledgment/Financial Support:
Sincere thanks to Anhui Natural Science Foundation (No. 1608085MH164) for providing funds for this study.

Declaration of Interest:
The authors have no conflicts of interest to report.

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