

# Effect of Hepatitis B Virus (HBV) Infection on Lipid Profile in Ghanaian Patients

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## ABSTRACT

**BACKGROUND:** Worldwide, approximately 257 million people have chronic hepatitis B virus (HBV) infection, with the highest infection rates recorded in Africa and Asia. Although HBV infection has been associated with dyslipidemia, which may lead to death via liver related complications, the effect of the virus on the lipid profile of patients remain unclear. This study was designed to evaluate the effect of chronic hepatitis B virus infection on lipid profile of sero-positive individuals from Ghana.

**METHODS:** Blood samples were collected from chronic HBV infected patients who were recruited from the Korle-Bu Teaching Hospital, Accra, and HBV sero-negative healthy volunteers who were used as controls. Demographic and clinical data were obtained using a structured questionnaire. Blood pressure and body mass index were determined, and HBV profile markers and lipid profiles of the patients were determined using a commercially available kit and a chemistry analyzer, respectively.

**RESULTS:** Triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL), very low density lipoproteins (VLDL), and total cholesterol were used as indices of lipid metabolism disorder. Body mass index and diastolic blood pressures were significantly elevated in patients compared to healthy volunteers.

**CONCLUSION:** The observed high total cholesterol and LDL, with a significantly lower HDL levels compared to healthy controls suggest an increased cardiovascular disease risk index in the patients. There is therefore the need to regularly monitor HBV infected patients for signs of cardiovascular diseases.

**KEYWORDS:** lipid metabolism, lipoproteins, cholesterol, triglycerides, hepatitis B virus (HBV)

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## Introduction

Hepatitis B Virus (HBV) infection is a global health menace with over 2 billion people living with the virus worldwide, and 257 million people suffering from the chronic stage infection.<sup>1</sup> WHO estimated that about 1.34 million HBV infected patients in 2015 died due to chronic hepatitis, cirrhosis, and hepatocellular carcinoma, and other liver-related complications, and the infection has been found to cause epidemics in most parts of Asia and tropical African countries.<sup>1</sup>

HBV belongs to a group of hepatotropic DNA viruses called the Hepadnaviruses. The virus infects mainly the liver of the host, mostly humans, and causes an inflammation of the organ.<sup>2</sup> HBV can be transmitted horizontally via sexual contact with an infected person, through the skin by contact with infected fluids, by inoculation with contaminated blood or blood products, by transplantation of organs from infected donors, and can be transmitted vertically from infected mothers to their offspring. Serum hepatitis B surface antigens (HBsAg) are mostly used as reliable indicators for HBV infection.<sup>3</sup>

The liver is involved in the sequestration, remodeling, and redistribution of lipid metabolites including low-density

lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and total cholesterol (T. chol).<sup>4,5</sup> High levels of LDL put more cholesterol in circulation, and therefore increasing plasma cholesterol levels. Cholesterol may accumulate in the arteries and result in a blockage of the blood vessels, thus increasing the risk of cardiovascular and coronary heart diseases. Mild to severe liver deranging factors such as chronic HBV infection could potentially interfere directly or indirectly with the levels of the circulatory lipids in the plasma of infected individuals.<sup>6,7</sup>

Hepatitis and liver damage arise as a consequence of immune response to the virus in the hepatocytes,<sup>8,9</sup> and chronic pro-inflammatory cytokine surge characterizes most cases of chronic hepatitis B infection, which could alter plasma lipid distribution.<sup>10</sup> Most pro-inflammatory cytokines generally increase lipogenesis, very low density lipoprotein (VLDL) production, and a consequent increase in circulating LDL levels in serum.<sup>11,12</sup> Reports on the profile of lipids in cases of liver diseases have been very diverse, showing slight to marked variations in plasma lipoprotein and apolipoprotein patterns.<sup>13</sup> Studies have reported minor to major increase in serum levels of apolipoproteins and lipoproteins in patients suffering from



various liver diseases.<sup>13-15</sup> In a study that investigated dyslipidemia in chronic hepatitis, TG and T. chol levels decreased with an increase in LDL, with HDL remaining fairly unchanged.<sup>16</sup> Su et al<sup>17</sup> reported a marked elevation of serum ALT as a correlate to lower levels of HDL in patients with asymptomatic chronic hepatitis B, and a correlate to higher TG levels in patients without HBV infection. In Ghana, the effect of chronic HBV infection on lipid metabolism has not been well studied, and hence it is difficult to clearly associate chronic infection with cardiovascular risk and liver damage. This study was therefore designed to determine the effect of HBV infection on lipid metabolism (lipid profile) in patients at the Korle-Bu Teaching Hospital, Accra, Ghana.

## Methodology

### *Study design and participants*

This is a cross sectional study, which was carried out at the Korle-Bu Teaching Hospital (KBTH), Accra, to evaluate the effect of chronic hepatitis B virus (HBV) infection on lipid profile. Institutional Review Board (IRB) clearance was obtained from the Noguchi Memorial Institute for Medical Research, University of Ghana, Legon (NMIMR-IRB CPN 071/14-15). Clinically diagnosed chronic HBV infected patients attending clinic at the Department of Gastroenterology, KBTH were recruited. A well-structured questionnaire was administered to 82 study participants (both case and control groups) to collect and analyze demographic variables. Exactly 22 subjects were excluded from the study based on one or more of the following criteria: persons diagnosed with dyslipidemia and/or some other liver complications, individuals with record of alcoholism, usage of drugs that affect the lipid profile in blood, pregnant women, and persons diagnosed with diabetes mellitus. Twenty-nine (29) patients (15 males and 14 females) without any of the above exclusion criteria were recruited as cases and 31 HBV sero-negative healthy volunteers (19 males and 12 females) were enrolled as controls.

### *Baseline measurements*

Mercury sphygmomanometer and stethoscope were used to measure systolic and diastolic blood pressures, respectively, after the patients have rested for at least 10 minutes. To calculate the body mass index (BMI) of the participants, the body weights and heights were measured by recording to the nearest 0.1 kg using an Omron digital weighing scale (Hoofdrop, Netherland) and a Seca 216 Accu-Hite stadiometer (Birmingham, England), respectively.

### *Sample collection and laboratory analysis*

Overnight fasting venous blood samples (5.0 ml) were collected using sterile vacutainer needles into sterile serum separator tubes, and the tubes were labeled with a unique identification

number for each participant. The blood samples were left for 5 minutes to clot and centrifuged at 3,000 rpm for 10 minutes using a TGL-16MC high speed refrigerated centrifuge (Gulfex Medical and Scientific, England). The serum obtained after centrifugation was aliquoted into 1.5 ml eppendorf tubes and stored at -20 °C until used for required tests and assays.

### *Determination of HBV profile markers*

The serum samples of the subjects were first screened to detect the presence of circulating HBV profile markers. HBsAg, antibody to HBsAg (anti-HBs), HBcAg, antibody to HBcAg (Anti-HBc), HBeAg, and antibody to HBeAg (anti-HBe) were assayed with Lumiquick commercial antigen-antibody test kits (Lumiquick Diagnostics Inc., Santa Clara, USA). The enzyme immunochemical assay visibly displays HBV antigen-antibody complexes as bands in their respective panels on the test kit. The appearance of a single visible band gives a negative test while the appearance of a double band indicates a positive result for a circulating HBV antibody or antigen as stated by the test protocol.

### *Serum lipid profile*

Serum lipid profile, including high density lipoprotein (HDL), total cholesterol (T. chol), low density lipoprotein (LDL), and triglycerides (TG) were determined using a Humalyzer Jnr. 18050 semi-automated chemistry analyzer (Human Diagnostica, Wiesbaden, Germany). T. chol and TG levels were determined using cholesterol and triglyceride reagents from Human Diagnostica (Wiesbaden, Germany), and HDL and LDL levels were determined using reagents from Diasys Diagnostic Systems (Hoizhem, Germany). VLDL levels (TG/2.2) and CVDR (T. Chol/HDL) were calculated. All the reagents and serum samples were left out to adjust to room temperature prior to analyses.

### *Statistical analysis*

Demographic and clinical data were expressed as mean  $\pm$  standard deviation (S.D), and statistical differences in the lipid profile indices among the test and control groups were analyzed using student t-test and ANOVA. All *p*-values < 0.05 were considered significant. A multiple regression analysis was used to determine the effect of age, TG, T. chol, HDL and LDL on CVDR of the patients.

## Results

The effect of HBV infection on lipid profile in patients attending the Korle-Bu Teaching Hospital was studied by screening for HBV infection and determining serum lipid levels of the patients and controls. The gender distribution, mean ages, blood pressure, and BMI of the case and control groups were not statistically significant (*p*-value > 0.05) (Table 1).

**Table 1.** Demographic data and clinical parameters of the study population.

PARAMETER	HBV PATIENTS (N=29)	CONTROL (N=31)	95% CI OF MEAN DIFFERENCE	P-VALUE (T-TEST)
Male	15 (51.7%)	19 (61.3%)		0.216
Female	14 (48.3%)	12 (38.7%)		
Age (yrs)	38.6 ± 10.0	37.2 ± 6.5	-2.95 – 5.73	0.520
DOI (months)	45.5 ± 39.1	–		
BMI (kg/m <sup>2</sup> )	26.7 ± 5.9	24.7 ± 8.1	-1.68 – 5.68	0.282
SBP (mmHg)	122.8 ± 14.4	117.0 ± 25.4	-4.97 – 16.57	0.286
DBP (mmHg)	74.8 ± 8.7	69.2 ± 16.2	-1.19 – 12.39	0.104

Values are presented as mean ± standard deviation. Independent t-test was used to compare HBV infected patients and sero-negative HBV controls.  $p < 0.05$  is considered statistically significant. CI= Confidence interval, N=sample size, DOI=duration of infection, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure.

**Table 2.** Serum-lipid profile of the study population.

PARAMETER	HBV PATIENTS (N=29)	CONTROL (N=31)	95% CI OF MEAN DIFFERENCE	P-VALUE (T-TEST)
T.chol (mmol/l)	3.9 ± 1.6	3.3 ± 0.5	0.01 – 1.20	0.052
TG (mmol/l)	1.07 ± 0.5	0.78 ± 0.4	0.06 – 0.52	0.016*
HDL (mmol/l)	0.90 ± 0.3	1.41 ± 0.5	-0.73 – (-0.30)	< 0.001*
LDL (mmol/l)	2.53 ± 1.5	1.54 ± 0.7	0.39 – 1.59	0.002*
VLDL (mmol/l)	0.22 ± 0.1	0.15 ± 0.1	0.02 – 0.12	0.009*
CVDR (mmol/l)	4.92 ± 3.2	2.70 ± 1.4	0.96 – 3.48	< 0.001*

Values are presented as mean ± standard deviation. Student t-test was used to compare HBV infected patients and sero-negative HBV controls. \*  $p < 0.05$  is considered statistically significant. T.chol=total cholesterol, TG=triglycerides, HDL=high density lipoprotein, LDL=low density lipoprotein, VLDL=very low density lipoprotein, CVDR=cardiovascular disease risk.

Comparison of the serum lipid profile of the study population revealed that there was no significant difference in the mean T. chol. levels for HBV infected patients and the control group. There were however statistically significant differences in the mean values of TG, HDL, LDL, VLDL levels and CVDR between the two study groups ( $p < 0.05$ ) (Table 2).

There was high detection frequency of HBsAg in the HBV infected patients with no detection of HBsAb. HBe and HBc antibodies were detected in about half of the infected patients; however, the HBe and HBc antigens were only detected in few patients (Figure 1).

The linear model indicated that T. chol and LDL increased the risk of cardiovascular diseases while TG and HDL decreased the risk (Table 3).

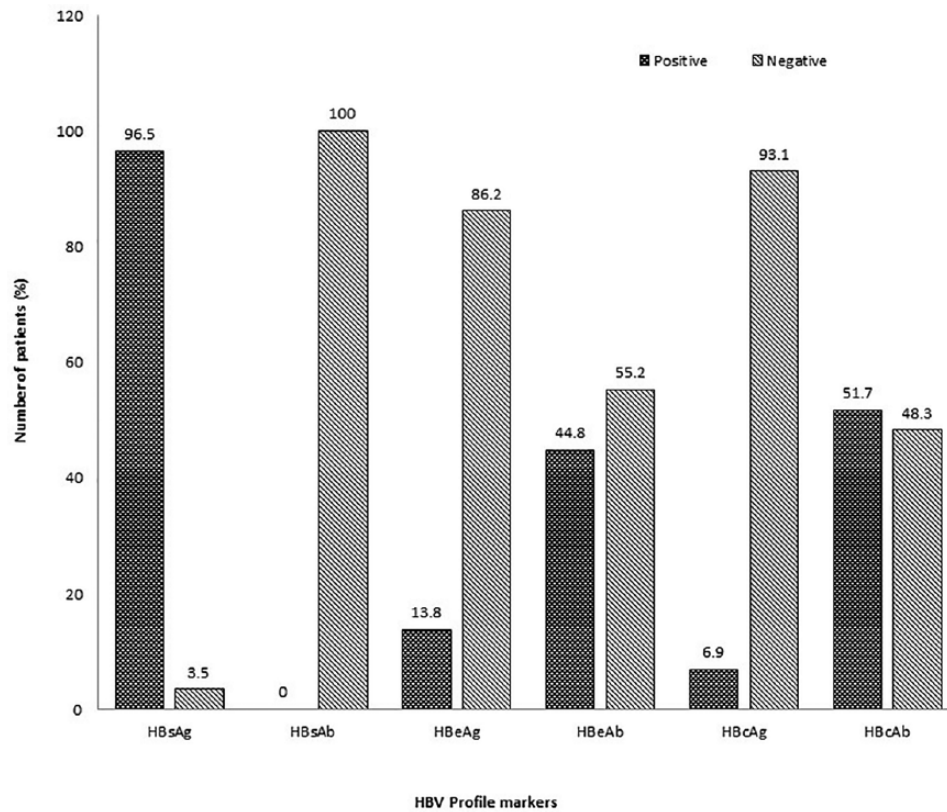
## Discussion

Dyslipidemia is one of the possible metabolic abnormalities associated with liver diseases.<sup>10</sup> Hepatocellular carcinoma (HCC) impairs metabolic processes, leading to alterations in plasma lipids and lipoproteins.<sup>15</sup> Under normal physiological

conditions, the human liver ensures homeostasis of lipid and lipoprotein metabolism.<sup>18</sup> HBV infection alters the synthesis of lipids in infected persons and the aberrations result in chronic hepatitis B infection.<sup>17</sup>

Our study showed that HDL levels were significantly decreased in the serum of the HBV-patients and consistent with what has been shown in a study in which HBV DNA levels were compared with HDL.<sup>19</sup> HDL and major apolipoproteins, apoAI and apoAII, were also reduced in patients suffering from cirrhosis or HCC due to chronic HBV infection.<sup>17,19</sup> The current study showed increased levels of TG, LDL and VLDL in the HBV infected patients compared to the control groups, and is consistent with findings reported by Nonogaki et al.<sup>20</sup>

Elevated LDL is an indicator of increased risk to cardiovascular related complications.<sup>21</sup> The linear model from the statistical analysis suggested that 71% variation in CVDR can be explained by age, T. chol, TG, HDL and LDL. The major contributor to CVDR were found to be age, T. chol and LDL. The observation of normal blood pressure in HBV infected patients and control in this study, is supported by the lack of statistical



**Figure 1.** Percentage frequency of Hepatitis B profile markers in the study participants.

HBV = Hepatitis B Virus, HBsAg = Hepatitis B surface antigen, HBsAb = Hepatitis B surface antibody, HBeAg = Hepatitis B envelope antigen, HBeAb = Hepatitis B envelope antibody, HBcAb = Hepatitis B core antibody.

**Table 3.** Correlation of serum lipids with cardiovascular disease risk.

	COEFFICIENT	STANDARD ERROR	T-VALUE	P-VALUE
T. chol	1.23	1.52	0.81	0.6202
TG	-0.84	1.13	-0.75	0.4253
HDL	-8.44	1.86	-4.54	0.0001*
LDL	0.14	1.60	0.09	0.9330

T. chol = total cholesterol, TG = triglycerides, HDL = high density lipoprotein, LDL = low density lipoprotein. \* *p*-values of < 0.05.

significance in the SBP and DBP measurements in the test and control groups.

A limitation in this study is the relatively smaller sample sizes that were used for the test and control groups. Even though we are cognizant of the fact the sample size can influence the over interpretation of the result, we are also of the view that the trends shown in this study will contribute to the understanding of the effect of hepatitis B virus (HBV) infection on lipid profile in patients in Ghana.

## Conclusion

Even though HBV infected patients did not show significant differences in blood pressure compared to negative controls, observed amounts of lipids in the patients suggests that HBV infection does lead to alterations in lipid biosynthesis.

The infection resulted in elevated serum T. chol, LDL and VLDL levels, and contributed to high risk of contracting cardiovascular diseases in Ghanaian patients as the infection progresses. There is therefore the need to regularly monitor HBV infected patients for signs of cardiovascular diseases.

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## Author Contributions

Concept and Design of Study was by OQ and EAT; Acquisition of Data was by BGA, SMA and EAT; Analysis and Interpretation

of Data was done by all the authors; Drafting of Manuscript was done by BGA and SMA; Critical Review of Manuscript was done by OQ and EAT; All the authors approved the manuscript.

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