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Changes in Lipid and Hematological Indices among Saudi Patients with Chronic Hepatitis B in the Makkah Region: A Case–Control Study

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Abstract
Objective: This study investigates hematologic and lipid abnormalities in chronic hepatitis B (CHB) patients to better understand its systemic effects and improve treatment strategies.
Methods: We compared 226 CHB patients to an equivalent number of non-HBV individuals between 2015 and 2021 in this retrospective study. Patient data were obtained from the Ministry of National Guard Health Affairs-Western Region (MNGHA-WR) database. Categorical data was analyzed using a chi-square test, while numerical variables were tested using a t-test with a significance threshold of $P < 0.05$. Age and gender adjustments were made to ensure the comparability of the results.
Results: The sex distribution of the CHB and non-HBV groups was comparable ($P = 0.51$), although non-HBV individuals were significantly older than those with CHB. CHB patients had significantly lower levels of HDL, TC, TG, WBC, RBC, PLT, Hgb, and MCHC, as well as decreased HCT and MCV, compared to non-HBV patients ($P < 0.05$). These differences persisted statistically significant even after adjusting for age and gender, except for TC and TG levels.
Conclusion: This study sheds light on the altered lipid and hematologic profiles of CHB patients as compared to non-HBV individuals. Our findings may help us better understand the extrahepatic consequences associated with CHB and establish an improved medical strategy for these patients.
Keywords: Hepatitis B virus, lipid abnormalities, hematological parameters, low platelet count, HDL, viral infection, thrombocytopenia, metabolic, chronic liver disease, CHB, HBV

Introduction

Despite the effectiveness of the hepatitis B virus (HBV) vaccine and extensive global immunization programs, HBV infection remains a significant health problem worldwide, limiting the WHO's ambitious goals.[1] An estimated 2 billion individuals worldwide are affected by HBV. For the year 2022, the WHO states that 254 million individuals were living with chronic hepatitis B (CHB), with 1.2 million new infections occurring each year. Unfortunately, these infections lead to 1.1 million deaths each year, primarily due to liver cirrhosis and hepatocellular carcinoma (HCC).[2] The Kingdom of Saudi Arabia (KSA) has the highest HBV infection rate in the Middle East.[3] According to a recent systematic study by,[4] around 1.3% of the Saudi population was infected in 2019.

HBV belongs to the *Hepadnaviridae* family and has a 3.2-kb double-stranded DNA genome. This genome has four overlapping open reading frames (ORFs): the polymerase gene (P), the surface gene (S), the pre-core gene (preC/C), and the X gene, all of which have reverse transcriptase activity.[5] The clinical presentation of HBV is highly variable and ranges from acute, inactive infections to severe chronic disease. Patients with chronic disease are more likely to develop severe health conditions such as cirrhosis or HCC.[6]

The liver is an important organ that regulates both exogenous and endogenous lipid metabolism.[7] It plays a crucial role in the production and regulation of essential lipid metabolites such as triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDLc).[8] The level of these metabolites in the blood is closely linked to liver function. As a result, CHB infection can significantly impair liver function, leading to abnormalities in lipid metabolism. Even mild liver damage can affect plasma lipid levels either directly or indirectly.[9] In addition to hepatic consequences, HBV infection also causes extrahepatic issues such as hematologic abnormalities, which frequently appear on diagnosis.[10] A complete blood count (CBC), which includes measurement of white blood cells (WBC), red blood cells (RBC), and platelets (PLT), is essential for understanding these consequences as it reflects the body's overall response to the infection.[11] Several studies, including those by,[11,12] suggest that viral hepatitis has a significant impact on certain blood parameters.

With this in mind, as well as the limitations of previous investigations performed in the western region, the present study aims to explore the impact of chronic HBV infection on lipid and hematologic parameters in patients from the MNGHA-WR cohort. This study might help identify biomarkers important for predicting complications related to CHB infection and to improve diagnostic tools.

Materials and Methods

Ethical Considerations

The study was approved by the institutional review board (IRB) of the King Abdullah International Medical Research Center (registration: SP19/499/J).

Study Population

CHB patients

This case-control study included 226 patients aged 9 years or older diagnosed with CHB infection. Accessible CHB patients were selected from the NGHA-WR database between 2015

and 2021. All patients were negative for both hepatitis C virus antibodies (anti-HCV) and human immunodeficiency virus (anti-HIV) antibodies and were naïve to antiviral treatment. Patients who had incomplete data or coinfection with either HCV or HIV were excluded from the study.

Non-HBV individuals

A total of 226 unmatched sex- and age-matched non-HBV individuals were selected from the MNGHA-WR database. Patients who were screened positive for hepatitis B surface antigen (HBsAg), anti-HCV, or anti-HIV were excluded. Random selection without replacement was used to verify that no non-HBV individuals were allocated more than once.

Demographic Features

We collected the available information in the electronic system of the MNGHA-WR which includes age, sex, and (within the national normal range) total cholesterol (TC ≤5.18 mmol/L), high-density lipoprotein-cholesterol (HDLc ≥1.55 mmol/L), triglycerides (TG <1.70 mmol/L), white blood cells (WBCs 4 ~ 11 × 10^9/L), haematocrit (HCT 40 ~ 54%), haemoglobin (Hgb 11.5 ~ 16.5 g/dL), mean corpuscular haemoglobin (MCH 27 ~ 32 Pg), mean corpuscular haemoglobin concentration (MCHC 32 ~ 36 g/dL), mean corpuscular volume (MCV 76 ~ 96 FL), platelets (PLT 150–450 × 10^9/L), and red blood cells (RBCs 3.8 ~ 5.8 × 10^{12}/L).

Sample Size Calculation

CHP patients' group were sampled with a control group consisting of individuals from the source population who did not have the outcome of interest (HBV). For sample size calculations, we used an unmatched case-control study (for which the case-control ratio was 1:1). Therefore, the minimum sample sizes required to detect a statistically significant difference were 226 CHB patients and 226 non- HBV individuals.

Statistical Analysis

In univariate analysis, associations between demographic parameters and metabolic abnormality characteristics were assessed across the case and control groups using the chi-square test for categorical data and the t test for numeric variables. Multivariate analyses adjusted for age and sex were also conducted to examine the differences between the case and control groups. Models were assessed using analysis of covariance according to the nature of our outcome. We checked assumptions of the linear relationship between the dependent variable and the covariate and homogeneity of regression slopes, and all models met the assumptions. *P* values were two-sided; all confidence intervals were 95%. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC). All tests were 2-sided, and $P < 0.05$ was used to indicate statistical significance.

Results

Demographic and Lipid Profile Characteristics

Lab investigations of 226 CHB patients and non-HBV individuals of the same size were compared according to the study's design (Table 1). Homogeneity of sex was observed in both groups ($P = 0.51$), and non-HBV individuals were significantly older than CHB patients were (mean ± SD; 70.3 ± 8.15 vs 62.3 ± 13.73 years). The mean TG, TC, and HDL levels were significantly lower in the CHB patients than in the non-HBV individuals (0.82 vs 2.75, 2.98 vs 4.57, 0.65 vs 1.08, respectively; $P < 0.05$).

Hematological Profile in Patients with HBV Infection

As shown in Table 2, the average WBC count was significantly lower in the CHB patients than in the non-HBV individuals (5.01 vs 7.39; $P < .0001$). Additionally, the average RBC count was significantly lower in the CHB patients than in the non-HBV individuals (3.41 vs 4.60), with significantly lower haemoglobin levels (9.74 vs 13.99), MCHC (24.12 vs 33.58), MCV (64.14 vs 86.22), and HCT values (30.01 vs 38.15) $P < .0001$. Similarly, for the platelet count, the average was significantly lower in the CHB patients than in the non-HBV individuals (247.62 vs 264.54; $P < 0.05$).

Multivariate Analyses Findings

After we adjusted for both age and sex as covariates, the regression analysis results shown in Table 3 and in the Figures 1 and 2 demonstrated that there were significant differences in hematologic and lipid profiles between the CHB patients and non-HBV individuals, as revealed by the bivariate analysis, except for the TG and TC levels, which showed no significant differences after we adjusted for age and sex ($P > 0.05$).

Table 1. **Demographic and lipid profile characteristics of CHB patients and non-HBV individuals at MNGHA-WR (Univariate analysis)**

Variables	CHB patients (*n* = 226)	non-HBV individuals (*n* = 226)	*P* value[2]
	n (%)[1]	n (%)	
Age, years, mean ± SD[3]	62.3 ± 13.73	70.3 ± 8.15	<.0001
Gender			0.51
Male (%)	129 (51.39)	122 (48.61)	
Female (%)	97 (48.26)	104 (51.74)	
	Mean (range)	Mean (range)	
HDL Mean (mmol/L)	0.65 (0.57, 0.73)	1.08 (1.04, 1.12)	<.0001
TC Mean (mmol/L)	2.98 (2.66, 3.31)	4.57 (4.40, 4.74)	<.0001
TG Mean (mmol/L)	0.82 (0.71, 0.94)	2.75 (0.11, 5.40)	<.0001

[1]"n" sample size, % percentage; [2]Chi-square test for categorical variables, and t test numeric variables; [3]Standard deviation.

Discussion

The liver regulates lipid metabolism at both the endogenous and exogenous levels.[13] It produces and reprocesses lipid metabolites such as HDLc, TC, and TG. The function of liver cells and tissues affects the level of these metabolites in plasma. CHB infection directly affects liver cell function. Mild to severe liver disruptors, such as CHB infection, are most likely to affect the level of these lipid substrates in the plasma, either directly or indirectly.[14] In the current study, there was a significant change in HDLc, TC and TG in CHB patients compared to the non-HBV group. This result is consistent with prior investigations.[15-18] These decreases might be explained by HBV's interactions with host lipid metabolism in several ways, including viral cell entry and the synthesis of a crucial viral protein, the HBV surface antigen. HBV gains entrance to hepatocytes via the Na+-taurocholate cotransporting polypeptide (NTCP), a peptide that normally allows for hepatocytes to take in host bile acids. HBV binding to NTCP reduces its capacity to promote bile acid uptake by hepatocytes. It leads to an increase in the process of converting cholesterol to bile acids.[14,19] However, after adjusting for age and sex in this study, the decreases in TC and TG were not significant.

Besides, liver also cause effect to the hematopoietic system which is an organ of several other organs in our body.[20] Lower WBC levels in patients with HBV may be the result of the virus attacking and destroying immune cells or an overactive immune response to infection. The impaired immune system of individuals with HBV infection cause by embezzles various illnesses and diseases.[21] According to the results of the recent study, those patients who were HBV positive had a lower WBC compared to non-HBV individuals with $P < 0.005$. This result is also supported from the previous research, in which a significant ($P < 0.05$) difference was found between WBC values of HBV infected patients comparing to healthy group as well.[21,22]

The PLT count is a critical indicator for assessing liver function, particularly in individuals with HBV infection.[23] Patients with CHB showed significantly decreased PLT levels compared to non-HBV people (P-value <0.05) which is consistent with the findings of.[24] The variation indicates

Table 2. **Hematological profile characteristics of CHB patients and non-HBV individuals at MNGHA-WR (Univariate analysis)**

Variables	CHB patients ($n = 226$)	non-HBV individuals ($n = 226$)	*P* value[1]
	Mean (range)	Mean (range)	
WBCs Mean ($\times 10^9$/L)	5.01 (4.48, 5.54)	7.39 (6.88, 7.90)	<.0001
RBCs Mean ($\times 10^{12}$/L)	3.41 (3.13, 3.70)	4.60 (4.51, 4.70)	<.0001
Hgb Mean (g/dL)	9.74 (8.94, 10.55)	13.99 (12.54, 15.45)	<.0001
PLT Mean ($\times 10^9$/L)	247.62 (232.88, 262.36)	264.54 (251.93, 277.15)	0.01
HCT Mean (%)	30.01 (27.57, 32.46)	38.15 (36.80, 39.50)	<.0001
MCH Mean (Pg)	18.30 (16.47, 20.13)	28.16 (27.81, 28.52)	<.0001
MCHC Mean (g/dL)	24.12 (22.23, 26.01)	33.58 (31.03, 36.13)	<.0001
MCV Mean (FL)	64.14 (59.00, 69.28)	86.22 (84.51, 87.95)	<.0001

[1]Chi-square test for categorical variables, and t test numeric variables.

Table 3. **Regression analysis for lipid and hematological profiles comparison of CHB patients and non-HBV individuals at MNGHA-WR (adjusted for age, gender)**

Variables	CHB patients vs. non-HBV individuals		*P* value CHB patients vs. non-HBV individuals[1]
	Beta coefficient (β)	Standard error (SE)	
HDL Mean (mmol/L)	−0.36	0.05	<.0001
TC Mean (mmol/L)	−1.41	0.23	0.22
TG Mean (mmol/L)	1.6	−0.88	0.37
WBCs Mean ($\times 10^9$/L)	−1.5	0.46	0.0009
RBCs Mean ($\times 10^{12}$/L)	−1.001	0.19	<.0001
Hgb Mean (g/dL)	−3.03	1.04	0.004
PLT Mean ($\times 10^9$/L)	−28.06	12.16	0.02
HCT Mean (%)	−6.73	1.75	0.0001
MCH Mean (Pg)	−8.21	1.17	<.0001
MCHC Mean (g/dL)	−6.69	2.01	0.0010
MCV Mean (FL)	−14.8	3.38	<.0001

1 ANCOVA was used to estimate differences in covariances across patients with CHB and without CHB, adjusted for age and gender, and the Kruskal–Wallis test for nonnormal numeric variables.

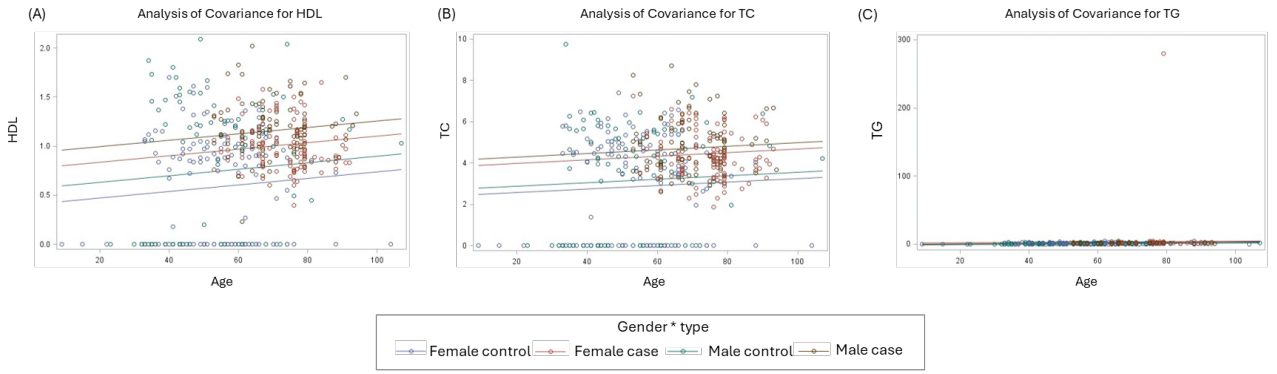

Fig. 1 **CHB patients' lipid indices compare with non-HBV individuals. The x- axis represents the age of subjects and y- axis represents lipid indices (A) HDL, (B) TC, and (C) TG.**

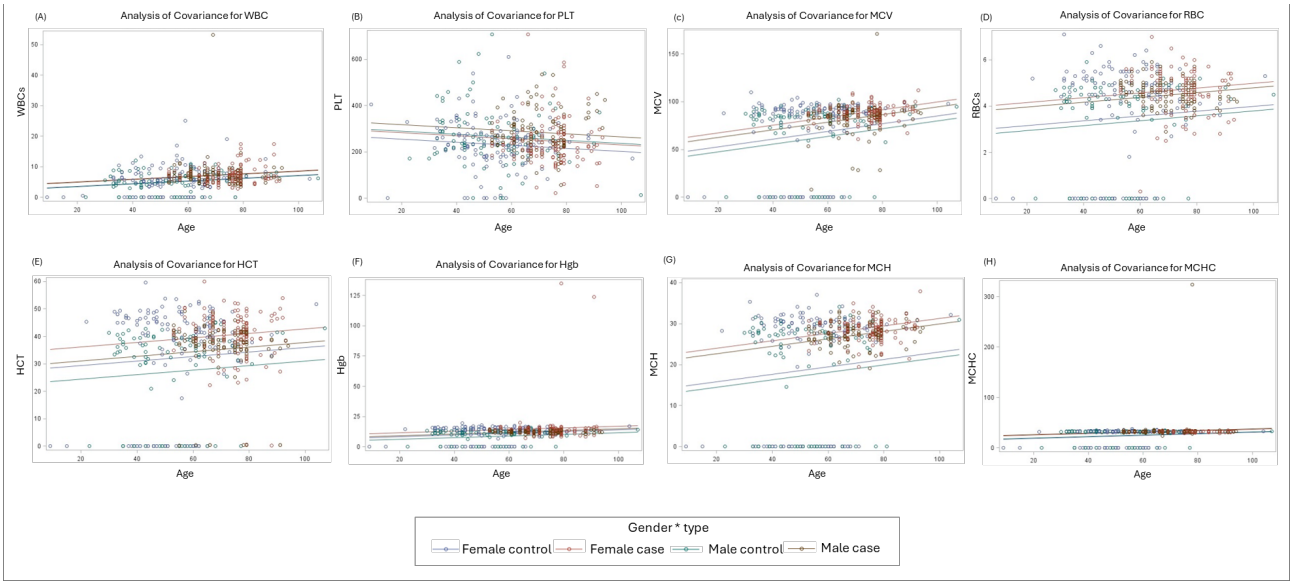

Fig. 2 **CHB patients' hematological indices compare with non-HBV individuals. The x-axis represents the age of subjects, and the y-axis represents hematological indices (A) WBCs, (B) PLT, (C) MCV, (D) RBCs, (E) HCT, (F) Hgb, (G) MCH, and (H) MCHC.**

that CHB patients are more probable to develop thrombocytopenia, which is characterized by low PLT levels, than individuals who do not have the infections.[25] Thrombocytopenia may cause severe bleeding in individuals with CHB infection, requiring immediate medical attention.[26,27] PLT are essential for blood clotting, which prevents blood loss from wounds and cuts. Low PLT levels may result in prolonged and difficult bleeding, potentially giving rise to significant consequences.[28]

MCV measures the average size of erythrocytes in the blood and is utilized for distinguishing between anaemia and other diseases. MCV has been proposed as an indicator of prognosis for negative outcomes in many diseases.[29] In this study a decreased of MCV count was observed among patients compared to non-HBV individuals with a *P*-value of <0.005. Similarly, RBC and Hgb levels were lowered in CHB patients, as reported by.[22,30] The study additionally revealed significant declines in HCT, MCH, and MCHC in CHB patients compared to non-HBV individuals. In contrast,[30] found that HCT and MCHC were slightly but not significantly different between CHB patients and non-HBV individuals. By contrast, MCH levels were greater in CHB patients.

Given HBV's major impact on hematological parameters, healthcare systems must emphasize early detection and ongoing surveillance. This includes promoting regular blood testing and using more effective serological screens that may detect HBV infections rapidly and monitor their impact on blood parameters regularly, particularly in high-risk individuals.[26]

There are several limitations to this study. For the first step, it adopted a retrospective case-control study from one center with 226 CHB individuals and equal subjects of 226 non-HBV as well. Second, additional parameters are required for further study and validation of the results. Third, the study did not account for different patients' statuses such as active and inactive HBV infection, liver cirrhosis, or HCC, which may affect the results. Also, the results may be less applicable to the broader population if they stem from a single center. Thus, studies aimed at following up on the applicability of such hematological and lipid parameters as diagnostic and prognostic markers are warranted.

Conclusions

The study demonstrated an association between chronic hepatitis B infection and alterations in lipid and hematological markers compared to those of non-HBV individuals. Several parameters, including high-density lipoprotein levels, total cholesterol levels, triglyceride levels, white blood cell counts, red blood cell counts, platelet counts, hemoglobin levels, hematocrit levels, mean corpuscular volume, mean corpuscular hemoglobin levels, and mean corpuscular hemoglobin concentrations, were significantly lower in CHB patients compared to non-HBV individuals. The statistically significant association persisted even after we adjusted for age and gender, except for total cholesterol and triglyceride levels, which did not vary substantially. These results shed light on the need for regular tests in these patients in addition to performing prospective investigations in our population to gain a better comprehension of this association between chronic hepatitis B infection and the alterations in these parameters, which could help in identifying and improving effective diagnostic tools that could assist in managing the complications in these patients.

Authors Contribution

Conceptualization, D.A., and N.B.; resources and data curation, D.A.; writing- original draft preparation, D.A.; writing- review and editing, A.K., B.A., N.B., and A.A.; supervision, A.K., and B.A.; funding acquisition, A.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

Ethical approval was obtained from the institutional review board of the King Abdullah International Medical Research Center under reference SP19/499/J. As the nature of the study, the ethics committee of King Abdullah International Medical Research Center waived the requirements for informed consent from patients.

Informed Consent Statement

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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