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The influence of chronic hepatitis B virus infection on fatty acid composition in erythrocyte membranes and plasma, and its effect on lipoxin A4 and resolvin D1 levels

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Abstract: Aim: This study aimed to assess the impact of chronic hepatitis B on fatty acids (FA) composition in erythrocyte membranes (RBC) and plasma, and its effect on lipoxin A4 and resolvin D1 levels.
Materials and Methods: Sixty participants were enrolled: 30 hepatitis B patients (15 with cirrhosis, 15 without) and 30 healthy controls. Fatty acids content in plasma and RBC membranes was analyzed by gas chromatography. Serum lipoxin A4 (LXA4) and resolvin D1 (RvD1) were measured via enzyme immunoassay. Principal component analysis (PCA) assessed correlations between fatty acid composition, LXA4 and RvD1 levels.
Results: Hepatitis B patients with cirrhosis exhibited significantly lower plasma lipoxin A4 (1812 pg/mL) compared to controls (2230 pg/mL) and non-cirrhotic hepatitis B patients (2453 pg/mL). Plasma n-3 FA levels (15.4% vs. 8.7%) and the n-3/n-6 ratio (0.8 vs. 0.4) were significantly reduced in cirrhotic patients. PCA data revealed associations between LXA4 and saturated fatty acids, and between n-3 FA and RvD1 pathways, suggesting disrupted lipid-mediated inflammation resolution. Erythrocyte membranes showed elevated trans C18:1 in cirrhotic hepatitis B.
Conclusions: Chronic HBV infection, especially with cirrhosis, alters fatty acid profiles and reduces lipoxin A4 level, contributing to persistent hepatic inflammation and highlighting potential lipid-targeted therapies.

Keywords: hepatitis B, fatty acids, lipoxinA4, resolvin D1, plasma.

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Introduction

Hepatitis B virus (HBV) is a member of the *Hepadnaviridae* family, classified into 10 genotypes (A–J) with over 40 subgenotypes [1]. HBV is highly infectious and environmentally resilient, with transmission primarily via blood, sexual contact, and perinatal routes [1]. Chronic infection affects approximately 350 million people worldwide, causing about one million deaths annually due to cirrhosis and hepatocellular carcinoma (HCC) [1].

The liver plays a central role in lipid metabolism, synthesizing and transporting cholesterol and fatty acids (FAs) in lipoprotein complexes. Liver diseases disrupt this balance, often reducing plasma cholesterol and triglycerides due to impaired lipoprotein synthesis [2–16]. Fatty acids, especially polyunsaturated fatty acids (PUFAs), modulate inflammatory responses in the liver, and dysregulated FA metabolism can exacerbate liver injury [4, 5, 8, 17, 18].

Emerging evidence shows that chronic HBV infection can directly influence hepatic lipid metabolism. Hepatic steatosis, characterized by triglyceride accumulation in hepatocytes, is observed in some HBV patients and increases susceptibility to oxidative stress, inflammatory cytokines, and apoptosis [4–8, 10, 19–29]. HBV viral protein X (HBx) plays a key role, modulating transcription, apoptosis, lipid accumulation, and viral replication [2, 3, 5–7]. HBx enhances expression of lipid-regulating transcription factors including liver X receptors (LXRs), sterol regulatory element binding protein 1 (SREBP1), and peroxisome proliferator-activated receptor γ (PPARγ), promoting lipogenesis and adipogenesis in hepatocytes [21–23].

Fatty acids also modulate HBV replication. Long-chain fatty acids (LCFAs) and fatty acid biosynthesis (FABS)-related enzymes are required for viral particle formation; inhibition of these enzymes reduces HBV DNA and HBsAg in vitro [25]. HBx upregulates FABS-related genes and enzymes critical for phosphatidylcholine synthesis, supporting viral envelope formation and viral persistence [22, 25].

Specialized pro-resolving mediators (SPMs), including lipoxin A4 (LXA4) and resolvin D1 (RvD1), are derived from PUFAs (arachidonic acid n-6 and docosahexaenoic acid n-3) and play a key role in resolving inflammation [17, 18, 27]. Altered PUFA profiles in chronic HBV infection may impair SPM production, contributing to persistent hepatic inflammation [26–29]. Despite this, few studies have comprehensively assessed plasma and RBC FA profiles together with LXA4 and RvD1 levels in HBV patients, especially in cirrhotic versus non-cirrhotic stages.

This study aimed to assess the impact of chronic hepatitis B on FAs composition in erythrocyte membranes (RBC) and plasma, and its effect on LXA4 and RvD1 levels.

Materials and Methods

Reagents

Butylated hydroxytoluene (BHT), 14% BF_3, and fatty acid methyl ester (FAME) standards were purchased from Sigma-Aldrich (St. Louis, MO, USA). Analytical grade chloroform, methanol, and n-hexane were obtained from Merck (Darmstadt, Germany). Gases for chromatography of 5.5 purity were purchased from AirLiquide (Poland).

Patients

Sixty participants were prospectively studied: 30 patients with chronic HBV infection (CHB; 21 men, 9 women; age 27–86, mean 54.1) treated at the Department of Infectious Diseases, Jagiellonian University Hospital, and 30 healthy volunteers (17 men, 13 women; age 18–74, mean 43). Among CHB patients, 15 had liver cirrhosis (LC) and 15 did not (HBV). Chronic HBV infection was defined as the presence of HBV-DNA for ≥6 months. Liver cirrhosis was confirmed via physical examination, lab tests, abdominal USG, elastography, and/or liver biopsy. Exclusion criteria included other acute or chronic inflammatory diseases. All patients had signed a filled informed consent to participate in the examination. The study complied with the Declaration of Helsinki and was approved by the Local Ethics Committee.

Sample collection

Venous blood samples were collected in K2-EDTA tubes. Erythrocytes were separated from plasma by centrifugation (1500×g, 10 min). 10 μL of 0.05% BHT was added to plasma samples to prevent oxidation.

Lipid analysis

Lipids were extracted from plasma with chloroform/methanol (2:1 v/v). FA methyl esters were synthesized using 14% BF_3 in methanol. Gas chromatography analysis was performed using an Agilent 6890N with FID at 260°C, column DB-23 (60 m × 0.25 μm), oven ramp 140–240°C, inlet 250°C, split ratio 40:1, injection 1 μL. FAs were identified using FAME standards. Results were expressed as relative percentages of total FAs. Total saturated (SFA), monounsaturated (MUFA), n-6 and n-3 PUFAs, trans-FAs, and n-3/n-6 ratios were calculated.

Biochemical analysis

Alanine aminotransferase (ALT) levels were assessed using standard laboratory methods.

RvD1 was measured using an ELISA competitive assay (Cayman Chemical, Ann Arbor, MI, USA) based on tracer binding to rabbit antiserum and spectrophotometric detection at 420 nm. LXA4 was quantified using an ELISA (EIAab, Wuhan, China) with pre-coated microplates and detection at 450 nm. Results were expressed in pg/mL.

Statistics

All data are presented as means ± standard deviation (SD) or medians and lower (Q_{25}) and upper (Q_{75}) quartiles. Normal distribution of variables was checked using the Levene test. Group differences were analyzed using F-test or Kolmogorov-Smirnov test. Correlations were assessed with Pearson or Spearman coefficients. Differences between study groups were determined using the one-way ANOVA and Scheffe *post hoc* test. PCA were performed on standardized variables with Euclidean distance. Statistical analysis was conducted using STATISTICA 13.1 (StatSoft Inc., Tulsa, OK, USA), with significance defined as $p \leq 0.05$.

Results

ALT, LXA4 and RvD1 levels

ALT was significantly elevated in all HBV groups compared to controls (p <0.01), with no difference between cirrhotic and non-cirrhotic HBV groups (Table 1).

Table 1. Comparison of ALT values in the study groups (median, Q_{25}–Q_{75}).

	Control (1) n = 30	HBV group (2) n = 30 mean	HBV (3) (without cirrhosis) n = 15 mean	HBV (4) (with cirrhosis) n = 15 mean	p
ALT (U/L)	19.4 (14–19.5)	35 (19–40)	40.4 (20–53)	30 (19–25)	1*vs*2 = 0.001 1*vs*3 = 0.006 1*vs*4 = 0.007 3*vs*4 = 0.74

LXA4 was significantly reduced in cirrhotic patients (1812 pg/mL) compared to controls (2230 pg/mL, p = 0.05) and non-cirrhotic HBV patients (2453 pg/mL, p = 0.001). No significant differences in RvD1 levels were observed (Fig. 1).

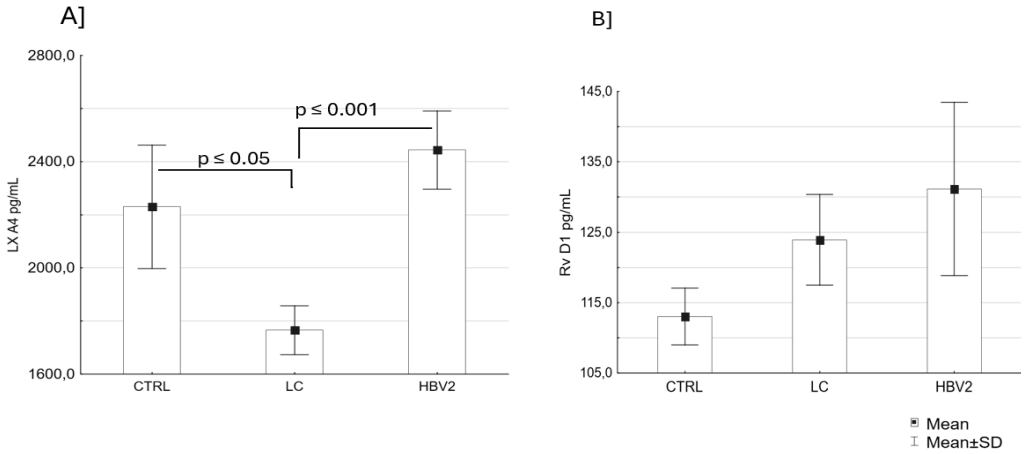


Fig. 1. Box-whisker plot showing differences in lipoxin A4 [A] and resolvin D1 [B] levels in plasma of patients with liver cirrhosis (LC) and HBV infection (HBV2) in comparison to control (CTRL).

Plasma fatty acid composition

Cirrhotic HBV patients had significantly higher C10:0 and C15:1, and lower C16:1c and C18:3n3 than controls. n-3 PUFAs were reduced (8.7% vs. 15.4%), and the n-3/n-6 ratio was lower (0.4 vs. 0.8, p <0.05) (Table 2).

Table 2. Fatty acid content [%] in plasma in the study groups. Means ± SD. MUFA, monounsaturated fatty acids; SFA, saturated fatty acids, PUFA — polyunsaturated fatty acids.

Fatty acid	Control (1) Mean ± SD	HBV total (2) Mean ± SD	HBV cirrhosis (3) Mean ± SD	HBV non-cirrhosis (4) Mean ± SD	P
C8:0	0.4 ± 0.2	0.9 ± 0.6	0.8 ± 0.5	0.9 ± 0.7	1 vs. 2 0.01
C10:0	0.3 ± 0.2	0.5 ± 0.3	0.6 ± 0.3	0.5 ± 0.3	1 vs. 2; 1 vs. 3 0.04
C12:0	1,1 ± 1.0	1.1± 0.8	1.3 ± 0.7	0.9 ± 0.8	
C14:0	2.2 ± 1.3	1.8 ± 0.7	1.8 ± 0.6	1.8 ± 0.8	
C15:0	1.5 ± 1.5	1.2 ± 1.4	0.9 ± 0.9	1.3 ± 1.7	
C16:0	16.0 ± 8.0	20.8 ± 6.3	21.6 ± 6.4	20.2 ± 6.4	
C17:0	5.7 ± 7.7	2.7± 2.6	3.0 ± 6.7	2.4 ± 4.7	
C18:0	7.5 ± 4.0	8.7 ± 2.9	8.3 ± 9.0	9.0 ± 2.8	
C22:0	0.5 ± 0.9	0.1 ± 0.1	0.2 ± 0.7	0.1 ± 0.1	
SFA	35.2 ± 5.7	37.9 ± 5.2	38.6 ± 4.8	37.2 ± 5.5	
C14:1n-5	2.1 ± 1.3	2.7 ± 1.4	3.0 ± 1.2	2.5 ± 1.5	
C15:1n-10	3.1 ± 2.9	5.6 ± 4.9	6.8 ± 5.6	4.8 ± 4.2	
C16:1n-7	6.6 ± 4.0	3.7 ± 3.0	2.7 ± 1.8	4.5 ± 3.6	1 vs. 2 0.01; 1 vs. 3 0.02
C17:1n-7	1.5 ± 1.1	1.2 ± 0.8	1.0 ± 0.8	1.2 ± 0.8	
C18:1tn-9	0.4 ± 0.4	0.5 ± 0.6	0.4 ± 0.6	0.5 ± 0.7	
C18:1n-9	8.6 ± 2.2	9.4 ± 2.0	10.0 ± 2.1	8.9 ± 1.8	
C20:1n-9	2.0 ± 1.5	2.5 ± 1.4	3.0 ± 1.3	2.2 ± 1.5	
C22:1n-9	0.5 ± 0.8	1.2 ± 0.9	1.1 ± 0.9	1.2 ± 1.2	
MUFA	24.4 ± 3.9	26.5 ± 4.3	27.6 ± 4.3	25.4 ± 4.4	
C18:2n-6t	2.2 ± 3.5	1.3 ± 2.5	1.6 ± 3.1	1.0 ± 2.0	
C18:2n-6	4.6 ± 2.9	6.7 ± 4.0	6.6 ± 3.3	6.7 ± 4.5	
C18:3n-6	3.1 ± 3.6	3.6 ± 2.5	3.9 ± 2.2	3.3 ± 2.7	
C20:2n-6	2.4 ± 2.1	2.5 ± 2.0	2.9 ± 2.1	2.3 ± 1.9	
C20:3n-6	1.5 ± 1.3	1.0 ± 0.8	1.1 ± 1.0	0.9 ± 1.2	
C20:4n-6	10.1 ± 4.9	9.2 ± 3.6	8.1 ± 2.6	10.1 ± 4.1	
C22:2n-6	0.4 ± 0.8	0.1 ± 0.0	0.1 ± 0.1	0.1 ± 0.4	
C22:4n-6	0.8 ± 0.8	0.6 ± 0.6	0.5 ± 0.4	0.7 ± 0.6	
n-6	22.4± 5.9	23.5 ± 5.6	23.1 ± 5.3	24.0 ± 5.9	
C18:3n-3	7.1 ± 4.6	3.8 ± 2.0	2.5 ± 2.9	4.8 ± 5.3	1 vs. 3 0.03
C20:3n-3	2.3 ± 2.0	2.1 ± 1.6	2.0 ± 1.1	2.3 ± 2.0	
C20:5n-3	3.0 ± 1.6	2.4 ± 1.5	2.2 ± 0.7	2.5 ± 2.0	
C22:5n-3	1.2 ± 1.1	0.6 ± 0.9	0.4 ± 0.6	0.8 ± 1.0	
C22:6n-3	1.5 ± 1.5	1.4 ± 1.1	0.5 ± 0.5	1.3 ± 1.2	
n-3	15.4 ± 7.7	10.2 ± 7.0	8.7 ± 5.4	11.8 ± 8.6	1 vs. 3 0.02
n-3/n-6	0.8 ± 0.5	0.5 ± 0.3	0.4 ± 0.3	0.6 ± 0.4	
trans	2.5 ± 3.7	1.7 ± 2.2	1.9 ± 3.1	1.5 ± 1.3	

Erythrocyte membrane FA composition C18:1 trans was significantly elevated in cirrhotic HBV patients. Other FAs showed no significant differences (Table 3).

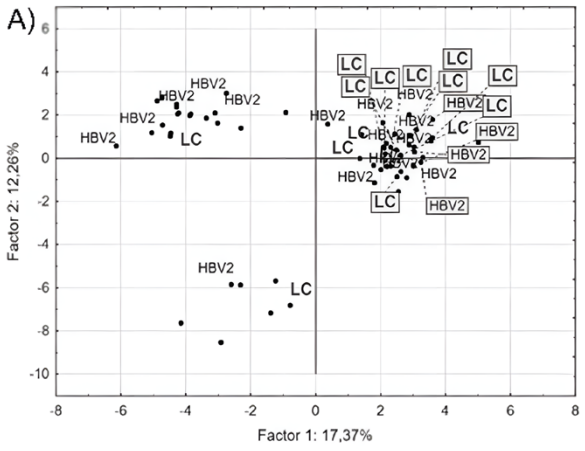
Table 3. Fatty acid content [%] in erythrocyte membranes in the study groups. Means ± SD. MUFA, monounsaturated fatty acids; SFA, saturated fatty acids, PUFA — polyunsaturated fatty acids.

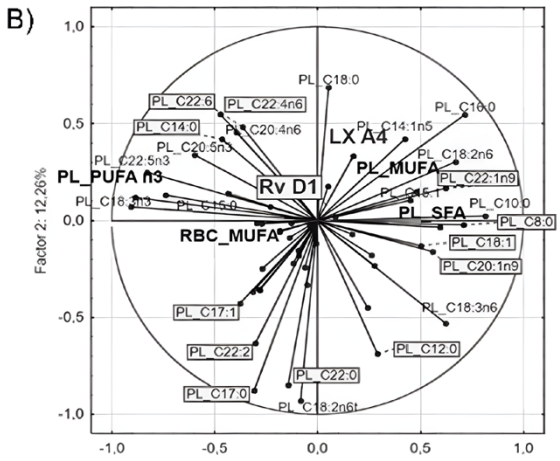
Fatty acid	Control Mean ± SD	HBV total	HBV cirrhosis Mean ± SD	HBV non-cirrhosis Mean ± SD	p
C14:0	3.5 ± 1.5	2.9 ± 1.0	2.8 ± 1.1	3.0 ± 0.9	
C16:0	26.2 ± 2.6	28.0 ± 3.8	27.9 ± 3.3	28.0 ± 4.2	
C18:0	22.7 ± 4.5	22.6 ± 4.9	21.7 ± 4.5	23.3 ± 5.2	
SFA	52.3 ± 6.2	53.4 ± 6.3	52.5 ± 6.2	54.3 ± 6.4	
C16:1n-7	1.6 ± 0.5	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.4	
C18:1tn-9	0.4 ± 0.1	1.1 ± 1.1	1.4 ± 1.1	0.8 ± 1.0	0.02
C18:1n-9	24.3 ± 3.6	22.3 ± 4.0	22.5 ± 4.1	22.1 ± 4.0	
MUFA	25.9 ± 3.8	23.7 ± 4.1	23.9 ± 4.2	23.5 ± 4.0	
C18:2n-6	10.2 ± 2.4	10.9 ± 3.1	11.2 ± 3.0	10.7 ± 3.3	
C20:4n-6	9.7 ± 7.9	9.5 ± 2.8	9.9 ± 2.9	9.2 ± 2.8	
C22:6n-6	0.2 ± 0.3	0.2 ± 0.2	0.2 ± 0.1	0.1 ± 0.3	
n-6	19.9 ± 7.4	20.4 ± 5.4	21.1 ± 5.2	19.8 ± 5.6	
C18:3n-3	0.8 ± 0.5	0.8 ± 0.6	0.7 ± 0.5	0.9 ± 0.7	
C20:5n-3	0.5 ± 0.7	0.4 ± 0.2	0.3 ± 0.4	0.5 ± 0.5	
n-3	1.3 ± 0.9	1.2 ± 0.7	1.0 ± 0.5	1.4 ± 0.9	
n-3/n-6	9.9 ± 7.8	9.6 ± 2.8	10.0 ± 2.9	9.3 ± 2.8	
trans	0.5 ± 0.7	0.4 ± 0.4	0.3 ± 0.4	0.5 ± 0.5	

Principal component analysis PCA presented clusters of cirrhotic patients with high saturated FAs and reduced n-3 PUFAs, correlating with lower LXA4 levels. Non-cirrhotic patients clustered closer to controls. These results suggest disrupted lipid-mediated resolution of inflammation (Fig. 2).

Discussion

Our study revealed significant alterations in fatty acid (FA) profiles in plasma and erythrocyte membranes in patients with chronic hepatitis B virus (HBV) infection, particularly in those with liver cirrhosis. The observed reduction in n-3 polyunsaturated fatty acids (PUFAs) and the decreased n-3/n-6 ratio suggest a disruption in the balance between pro- and anti-inflammatory mediators, potentially contributing to the persistence of chronic hepatic inflammation [18, 19, 26–29].





C)

Variable in plasma	Factor 1	Factor 2
LX A4		0.33
C8:0	0.71	
C10:0	0.81	
C12:0		-0.69
C14:0	-0.46	0.42
C15:0	-0.44	
C16:0	0.72	0.55
C17:0		-0.88
C18:0		0.69
C22:0		-0.85
SFA	0.60	
C14:1n-5	0.42	0.42
C15:1n-10	0.45	
C16:1n-9	-0.74	
C17:1n-7	-0.38	-0.43
C18:1n-9	0,50	
C20:1nn9	0.56	
C22:1nn9	0.62	
MUFA	0.48	
C18:3n-6	0.62	-0,53
C18:2n-6t		-0.93
C18:2n-6	0.67	
C22:2 n-6		-0.63
C20:4n-6	-0.40	0,46
C22:4n-6	-0.47	0.55
C18:3n-3	-0.89	
C20:5n-3	-0.60	
C22:5n-3	-0.83	
PUFA n-3	-0.91	

Fig. 2. Score plot in the principal component analysis (PCA). A) Cases projection on the factor 1 and 2 plane (1 × 2). Cases with sum of squared cosines ≥0.00 are presented. Unlabeled points refer to controls. Labels: HBV-herpes hepatitis virus; LC- liver cirrhosis; B) Variables projection on the factor plane. In the figure are marked variables showing correlations; C) Values of standardized factor-plasma variable coefficients obtained in PCA. Lx-lipoxin A4; PL — variable in plasma; RBC — variable in erythrocytes; Rv — resolvin D1.

Notably, changes in specific FAs, such as decreased C16:1c and C18:3n3, and increased C10:0 and C15:1, indicate a shift towards pro-inflammatory lipid species.

The reduction in lipoxin A4 (LXA4) levels in cirrhotic patients, alongside unchanged resolvin D1 (RvD1) levels, suggests differential regulation of specialized pro-resolving mediators (SPMs) during HBV infection. It is possible that n-3 PUFA deficiency limits RvD1 synthesis, whereas LXA4, primarily derived from arachidonic acid (n-6), is more sensitive to metabolic disturbances in cirrhosis. This distinction highlights the complex regulation of COX- and LOX-mediated SPM pathways and warrants further investigation [17, 18, 27].

Mechanistically, these changes are likely mediated through HBV X protein (HBx), which modulates the expression of transcription factors such as LXR, SREBP1, and PPARγ, as well as enzymes involved in FA biosynthesis [4, 6, 7, 10, 22, 26–29]. HBx promotes lipogenesis and triglyceride accumulation, supporting viral replication while increasing hepatocyte susceptibility to oxidative stress and inflammation. Additionally, disruptions in short-chain FA metabolism and gut-liver axis interactions may exacerbate lipid dysregulation in cirrhosis [26, 29].

Alterations in erythrocyte membrane FAs, particularly elevated C18:1 trans, may reflect systemic metabolic stress and oxidative imbalance, affecting membrane fluidity, immune function, and cellular signaling. These changes may influence both disease progression and host immune response to HBV [28].

Clinically, our findings have two major implications. First, FA profiles and LXA4 levels may serve as potential biomarkers for disease progression and complication risk, including hepatocellular carcinoma. Second, these results suggest therapeutic opportunities: supplementation with n-3 PUFAs or administration of LXA4/RvD1 analogs could enhance inflammation resolution and mitigate liver injury [29]. Previous clinical studies indicate that increasing n-3 PUFA intake can improve lipid profiles and support pro-resolving mediator synthesis, although data in the context of HBV are limited.

Nevertheless, our study has limitations: a relatively small sample size, age heterogeneity among participants, lack of dietary and lifestyle assessment, and single time-point measurements of FAs and SPMs, which limit causal inferences. Moreover, detailed virological parameters (HBV-DNA, HBeAg) were not included, which could influence lipid metabolism.

In conclusion, our observations indicate that chronic HBV infection, particularly in the setting of cirrhosis, leads to disturbances in FA composition and reduced LXA4 levels, potentially contributing to persistent inflammation and progressive liver damage.

Chronic HBV infection, particularly in patients with cirrhosis, is associated with significant alterations in plasma and erythrocyte membrane fatty acid composition and reduced levels of lipoxin A4. These changes likely contribute to persistent hepatic inflammation and impaired resolution, promoting progressive liver injury. Monitoring FA profiles and pro-resolving mediators may provide valuable biomarkers for disease progression. Moreover, targeting lipid metabolism and enhancing pro-resolving mediator pathways represent promising therapeutic strategies. Future longitudinal studies are needed to confirm causal relationships and assess the efficacy of such interventions in chronic HBV infection.

Authors contributions

The conception and design of the study, J.G.A., J.C.; Acquisition of data, J.G.A., A.P., J.C., P.W., A.B., A.J.; Analysis and interpretation of data, J.G.A., A.P.; Drafting the article, J.G.A., J.C., A.P., G.C.; Final approval of the version to be submitted: all Authors.

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Conflict of interest

None declared.

References

1. *Locarnini S., Hatzakis A., Chen D.S., Lok A.*: Strategies to control hepatitis B: Public policy, epidemiology, vaccine and drugs. J Hepatol. 2015; 62: S76–S86.
2. *Cho H.K., Kim S.Y., Yoo S.K., et al.*: Fatty acids increase hepatitis B virus X protein stabilization and HBx-induced inflammatory gene expression. *FEBS J.* 2014; 281: 2228–2239.
3. *Tang H., Oishi N., Kaneko S., et al.*: Molecular functions and biological roles of hepatitis B virus X protein. Cancer Sci. 2006; 97: 977–983.
4. *Hwang K.B., Kyaw Y.Y., Kang H.R., Seong M.S., Cheong J.*: Mitochondrial dysfunction stimulates HBV gene expression through lipogenic transcription factor activation. Virus Res. 2020; 277: 197842.
5. *You D.G., Cho Y.Y., Lee H.R., et al.*: Hepatitis B virus X protein induces size-selective membrane permeabilization through interaction with cardiolipin. Biochim Biophys Acta Biomembr. 2019; 1861 (4): 729–737.
6. *Zuo T., Jing S., Chen P., et al.*: Hepatitis B small surface protein hijacking Bip is initial and essential to promote lipid synthesis. J Proteomics. 2025; 311: 105358.
7. *Kim J.Y., Song E.H., Lee H.J., et al.*: HBx-induced hepatic steatosis and apoptosis are regulated by TNFR1- and NF-kappaB-dependent pathways. J Mol Biol. 2010; 397 (4): 917–931.
8. *Pais R., Rusu E., Ratziu V.*: The impact of obesity and metabolic syndrome on chronic hepatitis B and drug-induced liver disease. Clin Liver Dis. 2014; 18: 165–178.
9. *Yoon H., Lee J.G., Yoo J.H., et al.*: Effects of metabolic syndrome on fibrosis in chronic viral hepatitis. Gut Liver. 2013; 7: 469–474.
10. *Liu L., Li H., Zhang Y., et al.*: Hepatitis B virus infection combined with nonalcoholic fatty liver disease: Interaction and prognosis. Heliyon. 2023; 9 (1): e13113.
11. *Poortahmasebi V., Alavian S.M., Keyvani H., et al.*: Hepatic Steatosis: Prevalence and Host/Viral Risk Factors in Iranian Patients with Chronic Hepatitis B Infection. Asian Pac J Cancer Prev. 2014; 15: 3879–3884.
12. *Hu X., Wen Y.*: The hepatic steatosis, steatohepatitis and metabolic dysfunction: distinct roles in hepatocellular carcinoma occurrence in chronic hepatitis B patients. Hepatol Int. 2024; 18 (4): 1338–1339.
13. *Ates F., Yalniz M., Alan S.*: Impact of liver steatosis on response to pegylated interferon therapy in patients with chronic hepatitis B. World J Gastroenterol. 2011; 17: 4517–4522.
14. *Basaranoglu M., Basaranoglu G.*: Pathophysiology of insulin resistance and steatosis in patients with chronic viral hepatitis. World J Gastroenterol. 2011; 17: 4055–4062.
15. *Rastogi A., Sakhuja P., Kumar A., et al.*: Steatosis in chronic hepatitis B: prevalence and association with biochemical, histologic, viral, and metabolic parameters. Indian J Pathol Microbiol. 2011; 54: 454–459.
16. *Petta S., Camma C., Di Marco V., et al.*: Hepatic steatosis and insulin resistance are associated with severe fibrosis in patients with chronic hepatitis caused by HBV or HCV infection. Liver Int. 2011; 31: 507–515.
17. *Das U.N.*: Essential Fatty Acids and Their Metabolites in the Pathobiology of Inflammation and Its Resolution. Biomolecules. 2021; 11 (12): 1873.
18. *Dróżdż M., Gdula-Argasińska J., Biesiada G., et al.*: Clostridium difficile caused changes in fatty acids profile and resolvin D1 content in plasma of infected patients. Eur J Gastroenterol Hepatol. 2020; 32 (3): 318–324.
19. *Arain S.Q., Talpur F.N., Channa N.A., et al.*: Serum lipid profile as a marker of liver impairment in hepatitis B cirrhosis patients. Lipids Health Dis. 2017; 16: 51.

20. *Mandal S.K., Sil K., Chatterjee S., et al.*: A study on lipid profiles in chronic liver diseases. Nat J Med Res. 2012; 3: 70–72.
21. *Shi Y.X., Chen J., Yang Z.G.*: Impact of hepatitis B virus infection on hepatic metabolic signaling pathway. World J Gastroenterol. 2016; 22: 8161–8167.
22. *Kim K.H., Shin H.J., Kim K., et al.*: Hepatitis B virus X protein induces hepatic steatosis via transcriptional activation of SREBP1 and PPARγ. Gastroenterology. 2007; 132: 1955–1967.
23. *Shieh Y.S., Chang Y.S., Hong J.R., et al.*: Increase of hepatic fat accumulation by liver-specific expression of hepatitis B virus X protein in zebrafish. Biochim Biophys Acta. 2010; 1801: 721–730.
24. *Li H., Zhu W., Zhang L., et al.*: The metabolic responses to hepatitis B virus infection shed new light on pathogenesis and targets for treatment. Sci Rep. 2015; 5: 8421.
25. *Okamura H., Nio Y., Akahori Y., et al.*: Fatty acid biosynthesis is involved in the production of hepatitis B virus particles. Biochem Biophys Res Commun. 2016; 475: 87–92.
26. *Zhang L., Chen Q., Li H., et al.*: Altered fatty acid metabolism in chronic hepatitis B cirrhosis: implications for inflammation and liver injury. Front Immunol. 2025; 16: 1145678.
27. *Li X., Wang Y., Zhang M., et al.*: Role of specialized pro-resolving mediators in chronic liver disease. Liver Int. 2024; 44: 1234–1247.
28. *Wang H., Liu J., Chen Y., et al.*: Fatty acid metabolism in hepatic macrophages during chronic HBV infection. J Hepatol. 2024; 81: 879–891.
29. *Tezcan G.*: Therapeutic potential of pro-resolving lipid mediators in chronic hepatitis. Front Pharmacol. 2024; 15: 1154321.