Research Article

Hepatosteatosis and HBV seroclearance

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Hepatic steatosis is associated with HBSAG seroclearance in patients with chronic hepatitis B virus infection but it is also associated with disease progression

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Abstract

Background and Aim: The present study aimed to determine the effect of hepatic steatosis, as detected by liver biopsy, on Hepatitis B surface antigen (HbsAg) seroclearance and disease progression in patients infected with hepatitis B virus (HBV).

Materials and Methods: Patients with chronic HBV infection and chronic hepatitis B (CHB) from an existing cohort of HBV-infected patients were enrolled.

Results: This study included 296 patients: 186 with chronic HBV infection and 110 with CHB. Patients with chronic HBV infection were older (p=0.006), and exhibited a higher prevalence of wild-type mutants (p<0.001). At the baseline liver biopsy, 31% of the patients had hepatosteatosis. Thirty-two patients (11%) achieved HBsAg loss during the follow-up period; 72% had HBsAg seroconversion to anti-HBs. Multivariable Cox regression showed that the stage of HBV disease (chronic HBV infection vs. CHB) (Hazard ratio [HR]: 6.385, Confidence interval [CI]: 1.513–26.941, p=0.012) and grading of hepatosteatosis at baseline liver biopsy (HR: 4.699, CI: 1.662–13.286, p=0.004) were predictors of HBsAg seroclearance.

Conclusion: Hepatic steatosis was associated with a functional cure for chronic HBV infection; however, it also causes disease progression in HBV-infected patients.

Keywords: Hepatitis B virus; hepatosteatosis; HBsAg Seroclearance; metabolic dysfunction-associated steatotic liver disease.

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Introduction

Hepatitis B virus (HBV) infection is a major global public health concern, affecting over 250 million individuals.[1,2] HBV accounts for most adult cases of chronic liver disease (CLD), cirrhosis, and hepatocellular carcinoma (HCC) in Turkiye.[3–5] However, its proportion has decreased over time. An epidemiological study conducted in 2009 found that the prevalence of Hepatitis B surface antigen (HBsAg) was approximately 4%, and one in three individuals over the age of 18 years has experienced HBV. This study estimated that more than 2 million adults were HBsAg-positive in Turkiye.[6] The incidence of acute HBV infection in Turkiye has decreased significantly due to a successful HBV vaccination program initiated in 1992, as well as the implementation of a Viral Hepatitis Control and Prevention program in 2018.

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a public concern. MASLD affects an estimated 38% of adults around the world, causing considerable hepatic and extrahepatic morbidity and mortality.[7–9] The prevalence of MASLD is rising worldwide in parallel with obesity, diabetes, and metabolic disorders, showing a 50% increase from 1990 to 2006.[7] MASLD has become the most prevalent chronic liver disease, and the proportion of MASLD-related cirrhosis among patients on liver transplantation waiting lists has increased over the last three decades.[10–12] The frequency of MASLD ranged from 48% to 60% based on screening studies in Turkiye, placing the country among those with the highest prevalence of MASLD globally.[13] The prevalence of hepatic steatosis in patients with HBV infection is similar to that of the general population.[14,15] A recent meta-analysis of 54 studies found the prevalence of hepatic steatosis in patients with chronic hepatitis B (CHB) to be 32.8%.[16] Both chronic HBV infection and MASLD are common conditions. These two conditions are common types of chronic liver disease, and both can cause cirrhosis and its complications, and HCC. Therefore, it is of great importance to investigate the relationship between hepatic steatosis and chronic HBV infection.

HBsAg seroclearance can occur spontaneously in individuals with chronic HBV infections, ranging from 0.1% to 2.4%, with a nonlinear trend increasing over time.[17] HBsAg seroclearance is associated with sustained immune control of HBV and better clinical outcomes, including a lower risk of disease progression, decompensated cirrhosis, and liver-related death.[17,18] Several factors, including age, gender, serum HBsAg and HBV DNA levels, HBeAg status, disease stage, and antiviral therapy, affect HBsAg seroclearance.[17,18] The ideal goal of

Table 1. Characteristics of 296 HBV-infected patients at baseline

	Overall (n=296)	Patients with chronic HBV infection (n=186)	Patients with CHB (n=110)	p
Age (years)	54.6±12.1; 56.9 (24–81)	56.1±11.2; 58.6 (24–80)	53.2±12.7; 53.6 (24–81)	0.006
Gender (%) (male/female)	143/153	82/104	61/ 49	0.071
BMI (kg/m^2)	28.0±4.7; 27.7 (17–54)	28.2±5.1; 27.7 (17–54)	27.5±4.2; 27.7 (17–38)	0.797
Diabetes mellitus (%)	8.5	7.0	11.0	0.282
Hypertension (%)	34.4	39.6	22.7	0.019
HBeAg positive (%)	8.4	3.2	17.3	<0.001
Serum AST (U/L)	32.5±30.3; 24 (8–296)	25.0±12.7; 22 (8–94)	49.4±49.9; 33 (14–296)	<0.001
Serum ALT (U/L)	44.6±56.5; 27 (8–499)	28.9±26.7; 21 (5–192)	69.9±69.7; 46 (8–499)	<0.001
Serum GGT (U/L)	28.0±42.9; 19 (6–560)	22.2±17.6; 17 (6–560)	34.1±47.2; 21 (6–372)	0.002
Fasting glucose (mg/dL)	91.8±28.0; 86 (53–434)	89.1±12.7; 86 (66–156)	94.1±43.5; 86 (53–434)	0.777
Triglycerides (mg/dL)	123.1±62.6; 106 (39–409)	129.1±72.8; 113 (39–409)	117.8±58.6; 103 (48–311)	0.063
Total cholesterol (mg/dL)	186.8±39.5; 185 (66–287)	187.0±40.5; 184 (66–287)	184.0±35.2; 182 (111–256)	0.111
LDL (mg/dL)	115.6±31.8; 111.5 (30–224)	115.8±32.3; 110 (30–224)	113.6±28.2; 108 (62–197)	0.307
HDL (mg/dL)	46.1±13.1; 43(25–126)	45.4±11.8; 43 (25–90)	47.2±14.9; 44 (29–126)	0.885
VLDL (mg/dL)	24.5±12.5; 21 (8–80)	25.3±13.5; 22.2 (8–80)	24.2±13.0; 20.0 (10–73)	0.151
Total bilirubin (mg/dL)	0.8±0.5; 0.7 (0.1–4.8)	0.8±0.3; 0.7 (0.2–1.9)	0.8±0.7; 0.6 (0.1–4.8)	0.354
Albumin (g/L)	43.3±5.6; 44 (28–62)	44.3±3.3; 44 (35–54)	41.2±8.2; 42 (28–62)	<0.001
Platelet count (10^3/µL)	246±64.5; 235.5 (67–498)	242±57.2; 234 (67–399)	244±67.6; 233 (100–498)	0.847
INR	1.0±0.1; 1.0 (0.6–1.4)	1.0±0.1; 1 (0.6–1.4)	1.0±0.1; 1.0 (0.9–1.3)	0.05
FIB-4 score	1.29±1.28; 1.05 (0.6)	1.25±1.1; 1.0 (0.3–11.5)	1.36±1.6; 1.1 (0.3–15.2)	
Follow-up (months)	121.1±67.8; 137 (126.7)	126.4±71.2; 146	112.2±60.9; 122	0.008

HBV: Hepatitis B virus; CHB: Chronic hepatitis B; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; VLDL: Very low-density lipoprotein; INR: International normalised ratio. Mean±standard deviation, median (interquartile range).

antiviral treatment against HBV is the loss of HBsAg in serum. Unfortunately, with current oral antiviral treatment, HBsAg seroclearance rarely occurs after long-term therapy.[17] Data regarding the effect of hepatic steatosis on HBsAg seroclearance in patients with HBV infection are limited. Previous studies have reported that hepatic steatosis is associated with a higher rate of HBsAg seroclearance in chronic HBV infection.[19–22] However, most previous studies have relied on imaging methods to identify hepatic steatosis in HBV-infected patients. The aims of the present study were to determine the effect of hepatic steatosis, as detected by liver biopsy, on HBsAg seroclearance rates in patients with chronic HBV infection during long-term follow-up and to investigate whether the presence of hepatic steatosis is associated with disease progression in such patients.

Materials and Methods

Patients

This is a single-center, cross-sectional study. A total of 296 patients with chronic HBV infection and CHB from an existing cohort of HBV-infected patients who were seen at the Liver Diseases Outpatient Clinic were enrolled in the study. Chronic HBV infection was diagnosed based on the EASL guideline.[17] ICD-10 codes were used to identify patients with HBV infection. All patients with CHB received potent oral antiviral therapy at the physician's discretion. Data were collected from outpatient visit charts. This study was approved by the local ethical committee of Ankara University School of Medicine (2021/260). Our article was written in accordance with the Helsinki declaration.

Methods

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, and complete blood cell counts were measured by our central laboratory. Serological markers for viral infections (anti-HAV IgM, HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgG, anti-HCV, anti-HEV, anti-cytomegalovirus [CMV], anti-herpes simplex virus [HSV], and anti-Epstein-Barr virus [EBV]) were performed. Serum HBV DNA levels were determined using the Cobas Taqman assay (Roche Diagnostics, Branchburg, NJ, USA) with a lower detection limit of 20 IU/mL.

Table 2. The association between hepatosteatosis and HBsAg seroclearance

Grade of hepatosteatosis	Patients with chronic HBV infection (n=186)	Patients with CHB (n=110)	p	HBsAg seroclearance
No hepatosteatosis, <5%	69.9% (n=130)	66.4% (n=73)	0.816	6.4%
Grade 1, 5–33%	24.2% (n=45)	40.0% (n=30)		18.7%
Grade 2 and 3, >33%	5.9% (n=11)	6.4% (n=7)		27.8%

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; CHB: Chronic hepatitis B. 0=<5%; Grade 1 =5-33%; Grade 2 =33–66%; Grade 3 =>66%.

Histological Evaluation

Two pathologists (B.S., S.K.), blinded to the clinical and biochemical data, re-evaluated all liver biopsy specimens. The histological features of the samples were interpreted using the Ishak scoring system.[23] Accordingly, fibrosis was evaluated on a scale of 0–6, ranging from no fibrosis (score 0), to fibrosis beginning in portal areas (score 1), periportal fibrosis (score 2), porto-portal fibrosis (score 3), porto-central fibrosis (score 4), marked bridging fibrosis with occasional nodules (score 5), and progression to cirrhosis (score 6). Hepatocellular steatosis was graded on a scale of 0–3 based on the percentage of hepatocytes: 0=<5%, Grade 1=5%–33%, Grade 2= 33%–66%, and Grade 3=>66%.[24]

Definitions

HBsAg seroclearance was defined as the loss of detectable HBsAg for at least six months, with or without seroconversion to anti-HBs. The primary endpoint of the study was to investigate the effect of hepatic steatosis on HBsAg seroclearance in patients with chronic HBV infection.

The secondary endpoint aimed to determine the impact of hepatic steatosis on the disease outcome in such patients.

Follow-up

During the follow-up period, patients were regularly seen in an outpatient clinic. Laboratory tests were performed during this period. HBV markers and HBV DNA levels were serially monitored every three or six months.

Hepatic steatosis and liver stiffness were measured at the end of the follow-up period using a FibroScan probe (Echosens, Paris, France) with either an M or XL probe, which catered to patients with different body build types. Patients were examined after fasting overnight. The FibroScan probe was placed in the appropriate intercostal space window on the anterior axillary line. At least ten valid measurements were obtained within 5–10 minutes. The median ratio of 10 successive measurements to the interquartile range (IQR) was less than 30%. TE simultaneously measured the CAP (dB/m) and liver stiffness (kPa). Steatosis was classified as follows: none (CAP <248 dB/m), mild (CAP 248–267 dB/m), moderate (CAP 268–279 dB/m), and severe (≥280 dB/m).[25]

Statistical Analysis

Descriptive statistics are summarized as count and percentage for categorical variables, mean and standard deviations for normally distributed continuous variables, and median and interquartile range for ordinal and non-normally distributed continuous variables. The differences in proportions between groups were compared using the Chi-square or Fisher's Exact tests, where appropriate. The Mann-Whitney U test compared two groups regarding ordinal or non-normally distributed continuous variables. The Wilcoxon signed-rank test evaluated the difference between baseline and follow-up biopsies. The survival estimations were conducted using the Kaplan-Meier method, with group comparisons made using the Log-rank test. Cox proportional hazards regression was employed for both univariable and multivariable analysis. Variables with a p-value less than 0.25 in the univariable analysis and clinically important variables were included in the multivariable model using a purposeful selection approach. A p-value less than 0.05 was considered significant.

Results

This study included 296 HBV-infected patients: 186 with chronic HBV infection and 110 with CHB. At diagnosis, 92% of them were HBeAg negative. The median age of the patients was 56.9 years, with a predominantly female gender composition (52%). The median serum AST, ALT, and GGT levels were 24 U/L, 27 U/L, and 19 U/L, respectively. Nine percent of the patients had diabetes mellitus, and 34% had hypertension. The median glucose, triglyceride, cholesterol, and low-density lipoprotein (LDL) levels were 86 mg/dL, 106 mg/dL, 185 mg/dL, and 112 mg/dL (Table 1). Patients with chronic HBV infection were older (p=0.006), had a greater incidence of hypertension (p=0.019), exhibited a higher prevalence of wild-type mutants (p<0.001), and had lower baseline serum AST (p<0.001), ALT (p<0.001), and GGT levels (p=0.002) compared to patients with CHB (Table 1).

At the baseline liver biopsy, 93 (31.4%) patients had hepatosteatosis: 81% had mild, and the remaining 19% had moderate/severe hepatosteatosis. No significant difference in hepatosteatosis was observed between patients with chronic HBV infection and those with CHB (30.1% vs. 33.6%, p=0.399) (Table 2). The median follow-up period was 137.4 months (IQR=126.7).

Thirty-two patients (11%) achieved HBsAg loss during the follow-up period; 23 (72%) had HBsAg seroconversion to anti-HBs. Thirty patients had chronic HBV infection, while only two had CHB (16.1% vs. 1.8%, p<0.001). Patients with HBsAg seroclearance were older (p=0.001), had higher BMIs (p = 0.023), and had lower baseline serum ALT levels (p=0.022) compared to patients without HBsAg seroclearance. The characteristics of HBV-infected patients with and without HBsAg seroclearance are exhibited in Table 3.

HBsAg seroclearance commonly occurred in patients with hepatosteatosis compared to patients without hepatosteatosis (19/93, 20.4% vs. 13/203, 6.4%; p=0.001) (Table 2). The grade of hepatosteatosis at baseline liver biopsy affected HBsAg loss (Table 2). Multivariable Cox regression indicated that the phase of HBV infection-related disease (chronic HBV infection vs. CHB) (Hazard Ratio [HR]: 6.385, Confidence Interval [CI]: 1.513–26.941, p=0.012) and the grading of hepatosteatosis (HR: 4.699, CI: 1.662–13.286, p=0.004) were significantly associated with HBsAg seroclearance in HBV-infected patients

Table 3. Baseline characteristics of HBV-infected patients with and without HBsAg seroclearance

	Patients with HBsAg loss (n=32)	Patients without HBsAg loss (n=264)	p
Age (years)	61.1±8.2; 61.6 (45–76)	54.3±12.0; 56.5 (24–81)	<0.001
Gender (%) (male/female)	16/916	127/137	0.854
BMI (kg/m^2)	30.4±4.7; 30.4 (22–40)	27.6±4.7; 27.6 (17–54)	0.023
Diabetes mellitus (%)	12.5	8.0	0.496
Hypertension (%)	48	32	0.101
HBeAg positive (%)	0	9.5	0.089
Serum AST (U/L)	24.7±10.8; 20 (14–54)	36.0±36.8; 25 (9–296)	0.165
Serum ALT (U/L)	29.3±26.9; 18 (5–107)	47.3±54.6; 27 (10–390)	0.022
Abnormal initial serum AST (>40 U/L) (%)	6.3	19.3	0.086
Abnormal initial serum ALT (>40 U/L) (%)	21.9	31.1	0.316
Serum GGT (U/L)	24.8±12.2; 22 (10–51)	27.3±34.9; 19 (6–372)	0.370
Fasting glucose (mg/dL)	93.4±17.0; 94 (72–138)	90.9±30.4; 86 (53–434)	0.206
Triglycerides (mg/dL)	103.9±49.2; 92 (57–241)	126.6±68.8; 106 (39–409)	0.520
Total cholesterol (mg/dL)	172.6±30.0; 162 (135–222)	187.1±38.9; 185 (66–287)	0.903
LDL (mg/dL)	107.6±27.8; 103 (71–170)	115.6±30.9; 109 (30–224)	0.757
HDL (mg/dL)	43.2±15.2; 38 (26–90)	46.4±12.9; 43 (25–126)	0.233
VLDL (mg/dL)	21.2±9.8; 19 (10–48)	25.2±13.6; 21 (8–80)	0.723
Total bilirubin (mg/dL)	0.6±0.3; 0.6 (0.2–1.5)	0.8±0.5; 0.7 (0.1–4.8)	0.054
Albumin (g/dL)	44.3±2.9; 44 (38–48)	42.9±6.2; 44 (4–62)	0.813
Platelet count (10^3/µL)	242±42; 238 (164–332)	243±63; 233 (67–498)	0.973
INR	1.1±0.1; 1.0 (0.4–1.4)	1.0±0.1; 1.0 (0.6–1.3)	0.980
Follow-up (months)	102.3±65.2; 128 (7–203)	133.8±53.4; 141 (24–2227)	0.013
Chronic HBV infection CHB	30 (16.1%); 2 (1.8%)		<0.001

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; VLDL: Very low density lipoprotein; INR: International normalised ratio; CHB: Chronic hepatitis B.

(Table 4) (Fig.1a, b). HBsAg seroconversion to anti-HBs more commonly occurred in patients with HBV infection than in patients with CHB (11.3% vs. 1.8%, p = 0.003).

At the end of the follow-up period, the median serum AST, ALT, and GGT levels were 22 U/L, 22 U/L, and 18 U/L, respectively. The median glucose, triglyceride, cholesterol, and LDL levels were 92 mg/dL, 107 mg/dL, 185 mg/dL, and 114 mg/dL, respectively. The mean controlled attenuation parameter (CAP) and liver stiffness values using transient elastography (FibroScan) were 267.3±62.0 dB/m (median, 268 dB/m) and 6.2±2.7 kPa (median, 5.4 kPa), respectively. The mean FIB-4 score was 1.1±0.7 (median, 0.96).

Hepatic steatosis significantly affects disease progression. At the end of the follow-up period, the CAP and liver stiffness measurements detected by VCTE were significantly higher in those with hepatic steatosis compared to patients without hepatic steatosis (p=0.004 and p<0.001, respectively) (Table 5). Fibrosis progression was observed in patients with CHB who achieved virological remission under antiviral therapy. Liver stiffness was significantly increased in CHB patients with hepatic steatosis compared to those without hepatic steatosis (p<0.0001) (Table 5).

Discussion

This is the largest long-term follow-up single-center cohort study investigating the impact of biopsy-proven hepatic steatosis on HBsAg seroclearance and disease outcome in HBV-infected patients. HBsAg seroclearance is considered stable remission and a functional cure in the natural history of HBV infection. Liver biopsy is still the gold standard diagnostic method for diagnosing and assessing hepatic steatosis.[26] This study highlighted that the stage of HBV disease and hepatic steatosis significantly affect HBsAg seroclearance in patients with chronic HBV infection. Moderate and severe hepatosteatosis were more likely associated with HBsAg seroclearance.

Data regarding the mechanism by which hepatic steatosis influences HBsAg seroclearance are not well understood. Previous studies demon-

Table 4. Cox regression analysis revealed factors associated with HBsAg seroclerance

	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	P
Stage of HBV disease CHBV infection vs CHB	6.693	1.590–28.176	0.010	6.385	1.513–26.941	0.012
Age (>50 years)	9.726	1.316–71.871	0.026	7.125	0.985–53.003	0.055
Sex female vs male	1.078	0.533–2.181	0.834			
AST ≥40 U/L	2.709	0.644–11.387	0.174			
ALT ≥40 U/L	1.427	0.610–3.335	0.412			
GGT ≥50 U/L	2.100	0.286–15.423	0.466			
Hepatosteatosis			0.005			
Grade 1 vs Grade 0 (5–33% vs <5%)	2.452	1.117–5.382	0.025	2.513	1.144–5.520	0.022
Grade 2, 3 vs Grade 0 (≥34% vs <5%)	4.905	1.741–13.823	0.003	4.699	1.662–13.286	0.004

HBsAg: Hepatitis B surface antigen; HR: Hazard ratio; CI: Confidence interval; HBV: Hepatitis B virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; CHBV: Chronic hepatitis B virus; CHB: Chronic hepatitis B; 0=<5%, Grade 1 =5–33%, Grade 2 =33–66%, and Grade 3 =>66%.

Table 5. Hepatic steatosis affects disease outcome in patients with CHB who have achieved virological remission

	Patients with chronic HBV infection		p	Patients with CHB		p
	Hepatic steatosis	No steatosis		Hepatic steatosis	No steatosis	
FIB-4 score	1.14±0.46; 1.06 (0.5)	1.16±0.83; 0.96 (0.5)	0.458	1.14±0.46; 1.06 (0.5)	1.16±0.83; 0.96 (0.5)	0.120
Liver stiffness (kPa)	6.6±2.3; 6.1 (2.5)	5.7±2.0; 5.2 (2.4)	0.004	8.0±4.2; 6.8 (3.6)	5.9±2.9; 5.1 (1.9)	<0.0001
CAP (dB/m)	304.0±62.5; 316	257.6±61.7; 261	<0.0001	292.0±45.8; 295	247.3±55.6; 243	<0.0001

HBV: Hepatitis B virus; CHB: Chronic hepatitis B; CAP: Controlled attenuation parameter. Mean±standard deviation, median (interquartile range).

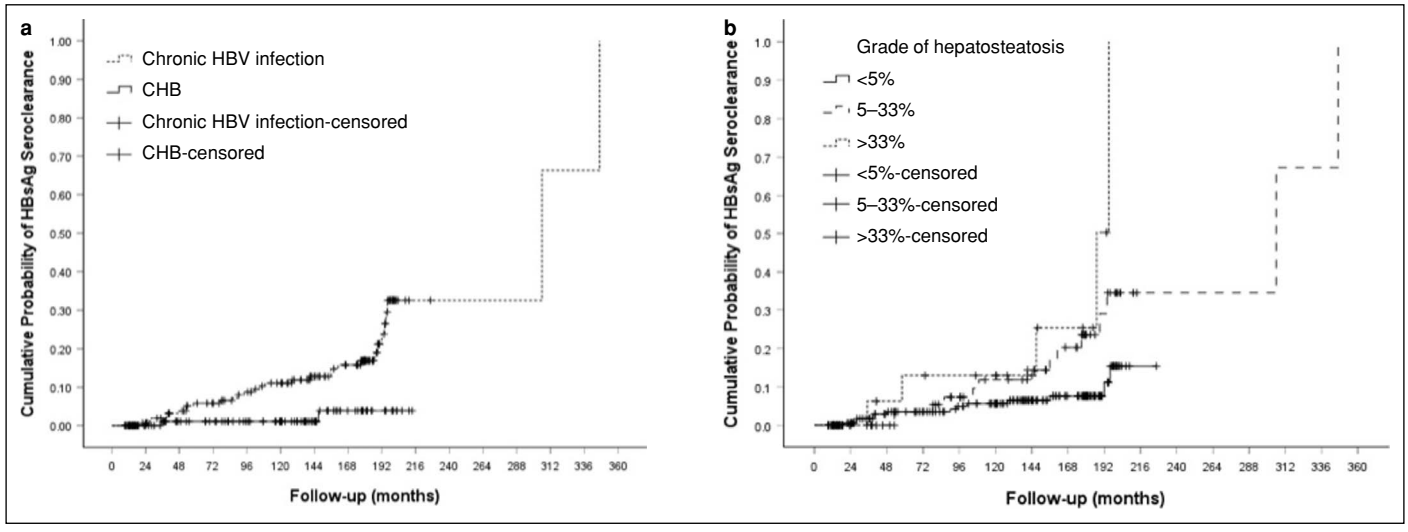

Figure 1. (a) Cumulative probability of HBsAg seroclearance in HBV-infected patients. **(b)** The grade of hepatosteatosis significantly affects HBsAg seroclerance.

strated that the presence of hepatic steatosis in patients with chronic HBV infection was associated with lower HBsAg and HBcAg levels in hepatocytes, as well as lower quantitative HBsAg levels in serum compared to those in patients with CHB.[16,19,27] A meta-analysis of six studies involving 3,870 patients with chronic HBV infection demonstrated that hepatic steatosis was significantly associated with a higher

rate of HBsAg seroclearance, with a pooled odds ratio of 2.22.[28] It was recently reported that combining low serum HBV DNA levels with hepatic steatosis led to significantly higher rates of HBsAg seroclearance.[20] It can be explained that intracellular fat alters the distribution of HBsAg in the cytoplasm of hepatocytes, leading to apoptosis, viral suppression, and ultimately HBsAg loss. Therefore, hepatic steatosis appears to be related to lower HBV replicative activity in patients with chronic HBV infection.

Chronic HBV infection is still a serious health problem and a significant cause of liver-related morbidity and mortality in the adult population of Turkiye.[4,5] Since the dramatically increasing prevalence of MASLD worldwide, chronic HBV infection and MASLD frequently coexist in Turkiye. This study confirms that over one-third of HBV-infected patients exhibited hepatosteatosis at baseline liver biopsy. Notably, there were no significant differences in hepatosteatosis prevalence between patients with chronic HBV infection and those with CHB. This prevalence is comparable to that of MASLD reported in Turkiye.[13]

The evidence regarding the impact of hepatic steatosis on HBV-related chronic liver disease, cirrhosis, and HCC is conflicting. Previous studies have shown that severe hepatic steatosis is associated with fibrosis progression, advanced fibrosis, developing cirrhosis, and HCC in patients with CHB.[19,20,29–32] However, some investigators have found no such association.[16] Dai et al.[32] recently demonstrated that chronic HBV infection with concurrent NAFLD is associated with greater severity of hepatic inflammation, ballooning, and advanced fibrosis. However, hepatic steatosis was not found to be a risk factor for significant or advanced fibrosis. The investigators concluded that hepatic steatosis could aggravate liver inflammation and fibrosis in patients with chronic HBV infection.[32] A meta-analysis reported that concomitant hepatic steatosis is associated with an increased risk of cirrhosis with a pooled OR of 1.52 and the development of HCC with a pooled OR of 1.59 in patients with CHB.[28] In a further subgroup analysis of this meta-analysis, hepatic steatosis did not affect the development of HCC in CHB patients who received antiviral treatment.[28]

Oral antiviral therapies against HBV infection cause viral suppression and reduce the risk of fibrosis progression, disease progression, and HCC development in patients with CHB.[17] In the present study, all CHB patients were treated with antiviral drugs and achieved viral suppression. Notably, fibrosis progression detected by VCTE was still observed at the end of the follow-up period in CHB patients with hepatic steatosis who were on oral antiviral therapy compared to those without hepatic steatosis. These findings indicate that concurrent hepatic steatosis contributes to the progression of hepatic fibrosis in patients with CHB who have achieved viral suppression.

In the present study, hepatic steatosis was demonstrated by liver biopsy in all participants at admission to prevent selection bias in the diagnosis of hepatic steatosis. However, in previous studies, hepatic steatosis has been diagnosed using different thresholds and various modalities, including abdominal sonography, transient elastography, computed tomography, and magnetic resonance imaging. These non-invasive diagnostic methods have different sensitivities in detecting hepatic steatosis.

The present study has several limitations. There is a lack of data on the anthropometric and detailed metabolic factors of patients, which affects the interpretation of the results. Additionally, no follow-up liver biopsies were conducted to assess the influence of hepatic steatosis on clinical outcomes in patients with CHB.

Conclusion

The stage of HBV disease and severity of hepatic steatosis contribute to HBsAg seroclearance in patients with chronic HBV infection. Hepatic steatosis can also accelerate fibrosis progression, especially in patients with CHB who have achieved virological remission under antiviral therapy.

Ethics Committee Approval: The Ankara University School of Medicine Clinical Research Ethics Committee granted approval for this study (date: 03.07.2021, number: 2021/260).

Informed Consent: Written informed consent was obtained from participants.

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