Major Article

Revista da Sociedade Brasileira de Medicina Tropical 47(2):158-164, Mar-Apr, 2014
http://dx.doi.org/10.1590/0037-8682-0009-2014

Clinical and laboratory characteristics associated with dyslipidemia and liver steatosis in chronic HBV carriers

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ABSTRACT

Introduction: Chronic hepatitis B virus (HBV) infection and liver steatosis (LS) are the most common causes of chronic liver disease, and their coexistence is frequently observed in clinical practice. Although metabolic syndrome is the main cause of LS, it has not been associated with HBV infection. The aims of this study were to describe the lipid profile and prevalence of LS among HBV carriers and to identify the characteristics associated with LS in this group. **Methods:** This retrospective cross-sectional study included hepatitis B surface antigen (HBsAg)-positive patients evaluated during 2011 and 2012. **Results:** Of the 83 patients included, the mean age was 46.4±12.5 years, 53% were men, and 9.1% were hepatitis B e antigen (HBeAg) -positive. These patients exhibited the following lipid profile: total cholesterol = 175.4±38.8mg/dL, low-density lipoprotein (LDL) = 113.0±32.7mg/dL, and triglycerides = 91.1±45.2mg/dL. Their fasting glucose was 95.3±14.5g/dL, and fasting insulin was 6.1±5.9µIU/mL. Liver steatosis was observed on abdominal ultrasound in 11.3% of individuals. Factors associated with the presence of LS included higher levels of total cholesterol, prothrombin activity, fasting insulin, and body mass index (BMI) as well as lower levels of aspartate aminotransferase (AST). **Conclusions:** These findings suggest that LS in patients with chronic HBV appears to be a consequence of metabolic alterations and insulin action rather than of viral factors.

Keywords: HBV. Hepatitis B. Fatty liver. Lipids. Cholesterol. Triglycerides.

INTRODUCTION

Chronic hepatitis B virus (HBV) infection and liver steatosis (LS) are the most common causes of chronic liver disease. An estimated 350 million individuals are chronically infected with HBV worldwide[1]. The lack of specific and sensitive noninvasive diagnostic tests for LS limits the ability to reliably detect the disease and determine its real prevalence. Often, non-alcoholic fatty liver disease (NAFLD) is diagnosed presumptively when imaging studies suggest the presence of LS or when elevated liver enzymes are noted in overweight or obese individuals with no other identifiable cause of liver disease[2]. For many patients, LS is indolent; however, approximately one-third of patients progress to cirrhosis and, in some cases, liver failure. Patients with simple LS may progress to steatohepatitis and cirrhosis[3].

It has been established that chronic hepatitis C is closely associated with LS, insulin resistance, and an increased risk of type 2 diabetes. Although these associations may be a consequence of metabolic factors, the hepatitis C virus itself has the capacity to promote steatosis and insulin resistance[4]. However, metabolic syndrome has not been associated with HBV infection[5,6].

It has been demonstrated that HBV carriers have decreased levels of total cholesterol, high-density lipoprotein, and low-density lipoprotein, suggesting that HBV infection counteracts dyslipidemia[7-10]. Moreover, LS in chronic HBV patients is associated with changes in anthropometric indices and metabolic factors but not HBV itself[11].

Factors affecting the development of LS in patients with chronic HBV infection remain obscure, although clinical observations report the common coexistence of both diseases[12,13]. Additionally, data are lacking on this subject in Brazil. This study aimed to evaluate the prevalence of LS and examine the lipid profiles of chronic HBV carriers, as well as to compare the clinical features and lipid profiles among individuals with chronic HBV infection with and without LS.

METHODS

This descriptive, retrospective cross-sectional study included consecutive adult patients who tested positive for hepatitis B surface antigen (HBsAg), presented at the Gastroenterology and

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Received 21 January 2014
Accepted 10 April 2014

Hepatology Outpatient Clinic of the University Hospital of the Federal University of Santa Catarina between August 2011 and September 2012, and provided their written informed consent to participate in the study. Patients with incomplete clinical or laboratory data in their medical records were excluded from the study. A diagnosis of hepatocellular carcinoma was also a cause for exclusion.

Clinical, laboratory, and histological findings were collected from data contained in the medical records. The patient records were analyzed for the following clinical and demographic characteristics: gender, age, comorbidities (diabetes mellitus, dyslipidemia, and hypertension), current antiviral therapy, and body mass index (BMI). The laboratory variables analyzed included the following: hepatitis B e antigen (HBeAg), hepatitis B virus-deoxyribonucleic acid (HBV-DNA), alpha-fetoprotein (AFP), creatinine, hemoglobin, platelets, prothrombin activity, albumin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, glycemia, fasting insulin, and glycated hemoglobin. Biochemical test results were expressed as absolute values. The hepatic biochemistry tests, including the levels of AST, ALT, ALP, and GGT, were expressed as a multiple of the upper limit of normal (×ULN). Laboratory tests performed within 6 months of the date of the ultrasound were used for this study. The levels of HBV DNA were measured using an in-house real-time quantitative polymerase chain reaction (qPCR) assay with a lower limit of detection of 20IU/ml. The most recent level of HBV-DNA was considered for inclusion in the study. Some patients were taking nucleos(t)ide analogues when their levels of HBV-DNA were tested.

Ultrasound data were collected from the medical records. An upper abdominal ultrasound is routinely performed for all patients positive for HBsAg to screen for hepatocellular carcinoma. A liver biopsy is indicated for all patients positive for HBeAg, regardless of their ALT levels. Patients negative for HBeAg with elevated ALT and/or a high viral load (≥ 2,000.0IU/mL) are also subjected to a liver biopsy. According to the National Consensus on the Classification of Chronic Hepatitis[14], the following histological characteristics were examined during the liver biopsies: advanced fibrosis (defined as structural changes of stage 3 or 4) and marked inflammatory activity (defined as periportal activity of stage 3 or 4).

Continuous variables were compared using Student's t test or the Mann-Whitney U test when appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. Univariate analysis was used to identify characteristics associated with the presence of liver steatosis (either on abdominal ultrasound or from the liver biopsy). The correlation between the liver biochemistry results and lipid profile (total cholesterol, HDL, LDL, and triglycerides) was assessed using Pearson's correlation coefficient. The level of statistical significance adopted was 5% (*p-value* < 0.05). All tests were two-tailed and conducted using the statistical software *Statistical Package for the Social Sciences* (SPSS) version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Ethical considerations

The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by the review board of the Federal University of Santa Catarina under the number 131.513.

RESULTS

Patient characteristics

From August 2011 to September 2012, 112 patients infected with HBV were considered for enrollment. Twenty-two individuals were excluded from the study due to lack of a lipid profile; four patients had no record of an abdominal ultrasound; and three had hepatocellular carcinoma **(Figure 1)**.

The characteristics of the 83 consecutive patients fulfilling the entry criteria are summarized in **Tables 1** and **2**. The mean age was 46.4±12.5 years; 53% of the patients were men; and 9.1% of the patients were HBeAg positive. The laboratory values, expressed as mean ± standard deviation (median), were ALT 0.9±0.1 (0.6) ×ULN, albumin 3.9±0.4 (3.9)g/dL, prothrombin activity 83.3%±14.9% (85.2%), and platelets 192,036.1±68,939.8 (182,000.0)/mm^3. The lipid profile results, expressed as mean ± standard deviation (median), were total cholesterol 175.4±38.8 (176.0)mg/dL, HDL 47.1±12.9 (45.0) mg/dL, LDL 113.0±32.7 (112.0)mg/dL, and triglycerides 91.1±45.2 (79.0)mg/dL. The fasting glucose was 95.3±14.5 (93.0)g/dL, fasting insulin 6.1±5.9 (4.1)µIU/mL, and glycated hemoglobin 6.0%±1.3% (5.7%). Steatosis of the liver was observed on abdominal ultrasound in 11.3% of the individuals. Among 39 individuals subjected to liver biopsy, steatosis was present in 41% (n = 16).

Correlation between liver biochemistry and lipid profile test results

A positive correlation was observed between the platelet count and total cholesterol (r=0.284; p=0.01) and LDL (r=0.35; p<0.01).

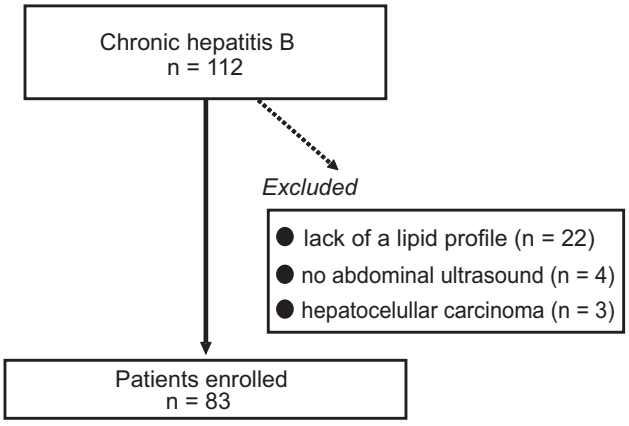

FIGURE 1 - Flow diagram of the potential candidates for participation in the study, criteria for exclusion, and subjects enrolled.

A positive correlation was also observed between serum albumin and total cholesterol (r=0.257; p=0.03) and LDL (r=0.34; p<0.01). Prothrombin activity was positively correlated with the total cholesterol (r=0.355; p<0.01) and triglycerides (r=0.296; p=0.02).

Negative correlations were observed between AST and total cholesterol (r=-0.314; p<0.01), HDL (r=-0.246; p=0.03), and LDL (r=-0.264; p=0.03). Negative correlations were also observed between direct bilirubin and total cholesterol (r=-0.396; p<0.01), LDL (r=-0.391; p<0.01) and triglycerides (r=-0.285; p=0.02).

No correlation was observed between ALT, ALP, GGT, and the lipid profile results or between HBV-DNA and the lipid profile results.

TABLE 1 - Clinical and laboratory characteristics of 71 patients with hepatitis B infection according to the presence of hepatic steatosis on ultrasonography.

Characteristics	Total n = 71	HS (+) n = 8	HS (-) n = 63	P value
Age (years)*	47.5 ± 3.1	45.4 ± 11.0	47.8 ± 13.4	0.63[t]
Male gender (%)	53.5	25.0	57.1	0.13[f]
Hypertension (%)	22.7	12.5	24.1	0.67[f]
Diabetes *mellitus* (%)	10.9	0.0	12.5	0.58[f]
Dyslipidemia (%)	9.4	12.5	8.9	0.57[f]
NUCs (%)	34.9	10.0	38.4	0.15[f]
lamivudine (%)	14.1	0.0	15.9	0.59[f]
adefovir (%)	2.8	0.0	3.2	1.00[f]
entecavir (%)	19.7	12.5	20.6	1.00[f]
tenofovir (%)	12.7	0.0	14.3	0.58[f]
BMI[§ a] (kg/m^2)	27.5	33.5	26.1	0.01[m]
Creatinine (mg/dL)[§]	0.9	0.9	0.9	0.83[m]
Hemoglobin (g/dL)*	14.3 ± 1.6	14.7 ± 1.0	14.3 ± 1.7	0.42[t]
Platelets ($/mm^3$)*	183,577 ± 64,744.3	213,250.0 ± 36,050.6	179,809.5 ± 66,800.6	0.17[t]
Serum iron (µg/dL)*	36.4 ± 92.2	48.1 ± 87.09	89.0 ± 36.5	0.82[t]
Prothrombin activity (%)*	83.0 ± 15.2	94.2 ± 8.3	81.4 ± 15.3	0.01[t]
Total protein (g/dL)*	7.2 ± 0.6	7.3 ± 0.4	7.2 ± 0.6	0.76[t]
Albumin (g/dL)*	3.9 ± 0.4	4.2 ± 0.4	3.9 ± 0.4	0.05[t]
HBeAg (%)	11.9	0.0	13.3	0.59[f]
AFP (ng/mL)[§]	1.9	1.6	1.9	0.37[m]
AST (xULN)[§]	0.7	0.5	0.8	0.01[m]
ALP (xULN)[§]	0.6	0.5	0.6	0.05[m]
GGT (xULN)[§]	0.4	0.3	0.4	0.23[m]
Direct bilirubin (mg/dL)[§]	0.1	0.2	0.1	0.88[m]
HBV-DNA (U/ml)[§ b]	5,675.0	2,970.0	6,758.5	0.87[m]
Advanced fibrosis[†] (%)	15.2	0.0	17.2	1.00[f]
Marked inflammatory activity[‡] (%)	28.1	0.0	32.1	0.30[f]

HS: hepatic steatosis; NUCs: nucleoside or nucleotide analogues; BMI: body mass index; HBeAg: hepatitis B e antigen; AFP: alpha-fetoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyltransferase; xULN: times the upper limit of normal; HBV-DNA: hepatitis B virus-deoxyribonucleic acid. *mean ± standard deviation; [§]median; [t]Student's *t* test; [m]Mann-Whitney U test; [f]Fisher's exact test; [†]advanced fibrosis = structural changes of stage 3 or 4; [‡]marked inflammatory activity = periportal activity of stage 3 or 4; [a]available in 19 patients; [b]available in 64 patients.

TABLE 2 - Lipid profile of 71 patients with hepatitis B infection according to the presence of hepatic steatosis on ultrasonography.

	Total	HS (+)	HS (-)	P
Characteristics	n = 71	n = 8	n = 63	value
Total cholesterol (mg/dL)*	173.8 ± 39.7	217.5 ± 41.2	168.2 ± 36.2	<0.01[t]
HDL (mg/dL)*	47.6 ± 3.5	45.6 ± 5.4	47.9 ± 14.2	0.40[t]
LDL (mg/dL)[§]	109.5	135.0	104.0	0.01[m]
Triglycerides (mg/dL)[§]	77.5	116.5	86.9	0.05[m]
Fasting glucose (mg/dL)[§ a]	93.0	98.0	93.0	0.86[m]
Fasting insulin (µIU/mL)[§ b]	3.5	9.2	3.3	0.03[m]
Glycated hemoglobin (%)[§ c]	5.8	5.8	5.7	0.75[m]

HS: of hepatic steatosis; HDL: high-density lipoprotein; LDL: low-density lipoprotein; * mean ± standard deviation; [§]median; [t]Student's *t* test; [m]Mann-Whitney U test; [a]available in 69 patients; [b]available in 31 patients; [c]available in 36 patients.

Factors associated with the presence of liver steatosis on abdominal ultrasound

Patients with LS, compared to those without steatosis on abdominal ultrasound, exhibited a higher mean total cholesterol (201.7±50.4 *vs*. 171.8±35.9mg/dL, respectively; p=0.02), greater prothrombin activity (94.1±7.9 *vs*. 81.6±15.1mg/dL; p<0.01), a higher median fasting insulin (9.2 *vs*. 3.3mg/dL; p= 0.04), and a higher median BMI (33.5 *vs*. 26.3kg/m^2; p=0.01). Patients with LS also showed lower median AST levels on abdominal ultrasound compared to those without steatosis (0.5 *vs*. 0.8 ×ULN, respectively; p=0.02) **(Tables 1** and **2)**.

No differences were found on ultrasound between individuals with or without LS with regard to age, gender, skin color, history of hypertension, diabetes or dyslipidemia, antiviral therapy, HBeAg, HBV-DNA, AFP, creatinine, hemoglobin, platelets, direct bilirubin, ALT, ALP, GGT, HDL, LDL, triglycerides, or fasting glucose (**Tables 1** and **2**). Neither the presence nor the absence of LS on abdominal ultrasound was correlated with advanced fibrosis or marked periportal inflammatory activity.

Factors associated with the presence of steatosis on liver biopsy

Only 39 individuals were subjected to liver biopsy. Only two of these patients were HBeAg-positive, and 16 (41%) presented LS on biopsy. When patients with steatosis were compared to those without steatosis on liver biopsy, no differences were observed with regard to age (p=0.59), gender (p=0.24), skin color (p=0.63), history of hypertension (p=1.00), diabetes (p=1.00), dyslipidemia (p=0.62), antiviral therapy (p=0.43), BMI (p=0.12), HBeAg (p=0.51), HBV-DNA (p=0.53), platelets (p=0.54), direct bilirubin (p=0.43), AST (p=0.19), ALT (p=0.82), ALP (p=0.23), GGT (p=0.93), total cholesterol (p=0.95), HDL (p=0.23), LDL (p=0.75), triglycerides (p=0.33), and fasting glucose (p=0.69). Neither the presence nor the absence of LS on biopsy was correlated with advanced fibrosis (p=0.37) and marked periportal inflammatory activity (p=0.94).

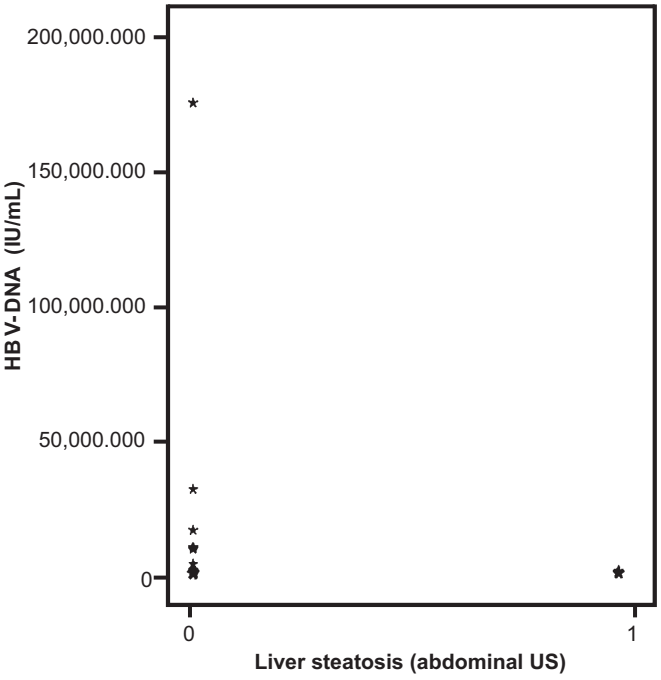

FIGURE 2 - Dispersion diagram illustrating the relationship between the HBV viral load and liver steatosis. HBV-DNA; hepatitis B virus-deoxyribonucleic acid; US: ultrasound.

The relationship between the HBV viral load and liver steatosis is illustrated in **Figure 2**.

Among those individuals with steatosis according to abdominal ultrasound, liver biopsy failed to confirm the diagnosis in one case **(Table 3)**. Among those without steatosis according to abdominal ultrasound, five steatosis cases were confirmed during the liver biopsy. Abdominal ultrasound demonstrated the following accuracy parameters: accuracy = 0.692, prevalence = 0.410, sensitivity = 0.313, specificity = 0.957, positive predictive value (PPV) = 0.833, and negative predictive value (NPV) = 0.667.

TABLE 3 - Distribution of 39 patients according to the presence of hepatic steatosis (HS) on ultrasonography and on liver biopsy.

Characteristics	HS (+) Bx (n = 16)		HS (-) Bx (n = 23)		Total (n = 39)	
	n	%	n	%	n	%
HS (+) on ultrasonography	5	31.3	1	4.3	6	15.4
HS (-) on ultrasonography	11	68.8	22	95.7	33	84.6

HS: hepatic steatosis; Bx: liver biopsy. p-value = 0.033.

DISCUSSION

Due to the global burden of obesity and increased body weight[15], LS has become a common medical problem. In Brazil, the prevalence of obesity has increased over time, from 2.2% for men and 7.4% for women in 1975 to 8.8% for men and 13% for women in 2003[16]. In 2010, 16% of the Brazilian population was obese. The prevalence of obesity is predicted to increase to 46% by 2050[17]. In the United States, the prevalence of obesity is higher than in Brazil, involving 32% of adults and 17% of young persons[18].

Among a sample of 90 Brazilian obese adolescents, the prevalence of LS on ultrasound was 15.5%[19]. Hepatic ultrasound is a simple, noninvasive technique that is widely used in clinical practice to detect fatty infiltration of the liver[20]. Several studies have assessed the sensitivity and specificity of ultrasound for detecting LS. In these studies, the sensitivity ranged from 60% to 94% and the specificity from 84% to 97%[21-24]. In a sample of 94 Brazilian individuals with elevated ALT, 40% presented LS on ultrasound, and both the BMI and history of diabetes were independently associated with the presence of LS[25]. Almost one-third of a sample of 2,287 American subjects evaluated by Browning et al. presented with LS according to magnetic resonance imaging (31%). LS was associated not only with metabolic syndrome but also particularly with obesity and insulin resistance[26].

In the present study, the presence of LS on abdominal ultrasound was associated with fasting insulin and total cholesterol, similar to findings previously reported by other authors in non-HBV patients[25,27-29], indicating that LS is related to disordered metabolism of blood glucose and lipids. Although BMI data were available only in a small subset of patients (n = 19), these data revealed a significant difference between the two study groups. Insulin resistance plays a central role in the pathogenesis of NAFLD. It has been demonstrated that obesity is associated with insulin resistance, leading to hyperinsulinemia, increased free fatty acid concentrations, and hyperglycemia. Insulin resistance leads to increased delivery of free fatty acids to the liver, increased fatty acid synthesis, and impaired release of triglycerides from the liver. These modifications cause triglycerides to accumulate in the hepatocyte[30].

A recent experimental study revealed that adenovirus containing the HBV genome (Ad-HBV) up-regulated the expression of genes related to cholesterol metabolism in HepG2 cells[31], suggesting that HBV itself influences cholesterol metabolism. Nevertheless, the lipid profiles among individuals with chronic HBV remain a matter of debate in the literature. When HBV carriers were compared to HBsAg-negative individuals, the HBV carriers exhibited significantly lower odds ratios for hypercholesterolemia and hypertriglyceridemia, as well as higher LDL cholesterol levels[9].

Biopsy-confirmed LS has been described in 18%-76% of chronic HBV patients[32-36]. The wide variation in the prevalence of LS in HBV carriers cannot be explained easily, as the patient characteristics do not appear to differ substantially among studies. No association was demonstrated between the histological findings of steatosis and dyslipidemia in the present study, similar to previous findings[33-37]. A possible limitation of the present study is that patients did not undergo biopsy specifically for this study. The data collection was retrospective, and the indication for liver biopsy was based on the viral load and ALT levels of the patients. Although this study design may indicate a source of *bias*, it represents a real-life approach to these cases. Nevertheless, as previously mentioned, abdominal ultrasound possesses high sensitivity and specificity for detecting LS, and in a sample of patients presenting more than 30% LS, the sensitivity and the specificity were shown to increase to 89.7% and 100%, respectively[24].

Among a sample of 350 individuals with chronic HBV in India, only the serum triglyceride level was found to be independently associated with LS according to multivariate analysis[36]. Other studies have indicated that patients with chronic HBV infection and LS had significantly higher BMI and higher levels of fasting glucose, triglycerides, and total cholesterol than did those without steatosis[11,13,32,35]. Based on these findings, we can surmise that it is important to closely monitor the BMI, insulin resistance, and lipid profile in patients with chronic HBV, as well as in the general population, to prevent the occurrence of LS. However, considering that a substantial amount of fatty infiltration in the liver may contribute to the seroclearance of HBsAg, it has been shown that HBsAg carriers with mild LS did not present an increased likelihood of HBsAg seroclearance. However, moderate-to-severe LS has been associated with 3- to 4-fold increased odds of HBsAg seroclearance compared to those with no evidence of LS[38].

No association was demonstrated between steatosis and either HBV DNA viral load or HBeAg status. Given the relatively small number of patients with viral load data (n = 64), this finding does not necessarily exclude a role for

HBV in mediating LS, and further studies that examine a larger cohort are needed to address this question. Some authors have found an association between viral load and the absence of steatosis[11,32], and an inverse relationship between metabolic syndrome and chronic HBV has been demonstrated[6]. The reason why HBsAg-positive subjects are less prone to developing metabolic syndrome remains unclear. One possible explanation is that individuals with a high BMI and moderate-to-intense ultrasound grading of LS tend to clear HBsAg from their serum.

In the present study, the level of AST was associated with the presence of LS on abdominal ultrasound. Aminotransferases are serum markers of liver damage that are usually altered in the presence of LS[39]. Despite observing lower levels of AST among patients with steatosis, both study groups presented altered AST levels. The association between LS and advanced fibrosis was not evaluated in the present study; nevertheless, it has been shown that LS is less common in patients with advanced fibrosis, and lower AST levels have been observed in individuals with advanced fibrosis[35].

Other possible limitations of the present study should be mentioned. Although the total number of patients included in the cohort was representative of the overall population, we examined possible associations between certain factors and LS, considerably reducing the number of subjects presenting particular variable combinations and, consequently, the power of the statistical tests. Although it is not a strict rule, maintaining a minimum of ten events per variable is recommended during logistic regression analysis. This recomendation is based on studies that showed increasing bias and variability, unreliable coverage of confidence intervals, and problems with model convergence as the events per variable declined below ten[40-42]. For this reason, these results need to be confirmed in a larger set of patients. Additionally, the study design was cross-sectional and did not include a longitudinal follow-up. The ultrasounds may not have been uniform in terms of operator and evaluation method, as this was not a prospective study. Indeed, the ultrasound results reflect a day-to-day medical practice in which one relies on ultrasound to initially define whether the patient presents with LS. As we have demonstrated, ultrasonography does not always match biopsy results perfectly. Data on alcohol ingestion, diet quality, and routine exercise were also lacking; therefore, an analysis of the effect of these variables on metabolic disease in this population was not possible. Another limitation of our study was the absence of a control group; nevertheless, our findings are comparable to previously published data.

The causes and significance of LS in HBV-related liver disease continues to be investigated. Individuals with LS present lower AST levels than do those without steatosis. The findings of the present study indicate that LS in HBV carriers appears to be a result of metabolic factors attributable to the host and related to insulin action rather than to viral factors; however, larger studies are needed to validate these findings. Therefore, it may be surmised that to prevent LS in patients with chronic HBV, AST and BMI should be periodically monitored and the blood glucose and lipid profiles should be controlled, in addition to educating these patients about healthy lifestyle, scientific dieting, and physical exercise.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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