Research Article

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Frequency of Hepatosteatosis and Relationship Between Laboratory Parameters and Hepatosteatosis in Chronic Hepatitis B Patients

Kronik Hepatit B Hastalarında Hepatosteatoz Sıklığı ve Laboratuvar Parametrelerin Hepatosteatoz ile İlişkisinin Değerlendirilmesi

Yasemin Çakır[1], Mehmet Ali Sungur[2], Murtaza Öz[1], Seyit Ali Büyüktuna[1]

[1]*Sivas Cumhuriyet University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Sivas, Turkey*
[2]*Düzce University Faculty of Medicine, Department of Biostatistics, Düzce, Turkey*

ABSTRACT

Objectives: Hepatosteatosis is very common worldwide and is defined as the accumulation of lipid droplets in hepatocytes. Hepatosteatosis is often associated with metabolic factors such as obesity, insulin resistance, and hypertriglyceridemia. The relationship between chronic hepatitis B (CHB) and hepatosteatosis remains unknown. We investigated the frequency of hepatosteatosis in patients with CHB and to evaluate the relationship between hepatosteatosis and laboratory parameters.

Materials and Methods: We retrospectively studied 262 patients with CHB. Patients were divided into two groups, hepatosteatosis and non-hepatosteatosis, according to liver ultrasonography findings. The groups were compared in terms of demographic characteristics and laboratory parameters.

Results: A total of 262 patients with CHB were included. The mean age was 45.1±15.3 years, 136 (51.8%) of whom were male. Liver biopsy was performed in 86 (32.8%) of the patients, 20 (7.6%) had fibrosis, and 163 (62.2%) had steatosis. Among the patients with steatosis, grade 1 steatosis was observed in 30.9 (81/163), grade 2 in 26 (68/163), and grade 3 in 5.3 (14/163). Hypertension, hepatomegaly, and cirrhosis were correlated with the presence of steatosis. Patients with steatosis were older than those without. Fasting glucose levels, low-density lipoprotein levels, and triglyceride levels of patients with steatosis were higher than those of patients without steatosis. High-density lipoprotein levels were lower in the steatosis group. No correlation has been found

ÖZ

Amaç: Hepatosteatoz, karaciğer enzim yüksekliğinin dünyadaki en yaygın nedenidir ve hepatositlerde lipid damlacıklarının birikmesi olarak tanımlanmaktadır. Hepatosteatoz, sıklıkla santral obezite, insülin direnci ve hipertrigliseridemi gibi metabolik faktörlerle ilişkilidir. Kronik hepatit B (KHB) ile hepatosteatoz ilişkisi ise halen gizemini korumaktadır. Bu çalışmanın amacı, KHB hastalarında hepatosteatoz sıklığının araştırılması ve hepatosteatoz varlığı ve şiddeti ile biyokimyasal, virolojik ve metabolik parametreler arasındaki ilişkinin değerlendirilmesidir.

Gereç ve Yöntemler: KHB tanılı 262 hasta retrospektif olarak incelendi. Hastalar karaciğer ultrasonografi bulgularına göre hepatosteatozu olan ve hepatosteatozu olmayanlar olarak iki gruba ayrıldı. Gruplar demografik özellikler ve laboratuvar parametreleri açısından karşılaştırıldı.

Bulgular: KHB tanılı 262 hasta çalışmaya dahil edildi. Hastaların yaş ortalaması 45,1±15,3 yıldı. Hastaların 136'sı erkekti (%51,8). 86 hastaya (%32,8) karaciğer biyopsisi yapılırken, 20 hastada (%7,6) fibrozis vardı. Hastaların 163'ünde (%62,2) steatoz vardı. Steatozu olan hastaların %30,9'unda (81/163) grade 1, %26'sında (68/163) grade 2 ve %5,3'ünde (14/163) grade 3 steatoz görüldü. Hipertansiyon, hepatomegali ve siroz steatoz varlığı ile korelasyon gösterdi. Steatozu olan hastalar steatozu olmayanlara göre daha yaşlıydı. Steatozu olan hastaların açlık kan şekeri, düşük dansiteli lipoprotein düzeyleri ve trigliserit düzeyleri steatozu olmayanlara göre daha yüksekti. Yüksek dansiteli lipoprotein düzeyleri steatoz

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Address for Correspondence: Yasemin Çakır MD, Sivas Cumhuriyet University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Sivas, Turkey
E-mail: yasemincakir2553@gmail.com **ORCID ID:** orcid.org/0000-0001-5510-3216 **Received:** 29.12.2023 **Accepted:** 26.02.2024

with gender, body mass index, hepatitis delta virus co-infection, hepatitis B virus (HBV)-DNA levels, or hepatitis B e antigen status between steatosis.

Conclusion: We found that hepatosteatosis is present in a significant proportion of patients with CHB. Although the presence of hepatosteatosis was associated with some metabolic parameters, the relationship between it and HBV parameters was not statistically significant.

Keywords: Cirrhosis, hepatitis B, non-alcoholic fatty liver diseases

grubunda daha düşüktü. Cinsiyet, vücut kitle indeksi (VKİ), hepatit delta virüs ko-enfeksiyonu, hepatitis B virüs (HBV)-DNA düzeyleri ve hepatitis B e antijen durumu ile steatoz arasında bir ilişki saptanmadı.

Sonuç: Çalışmamızda KHB hastalarının önemli bir kısmında hepatosteatoz eşlik ettiğini bulduk. Hepatosteatoz varlığı, non-alkolik yağlı karaciğer hastalığı için iyi bilinen risk faktörleri olan VKİ ve açlık glukoz seviyeleri ile ilişkili saptanırken HBV parametreleri ile arasındaki ilişki istatistiksel olarak anlamlı saptanmamıştır.

Anahtar Kelimeler: Siroz, hepatit B, non-alkolik yağlı karaciğer hastalığı

Introduction

Hepatitis B virus (HBV) infection affects millions of people worldwide (1). After an acute infection, the progression to chronic hepatitis B (CHB) increases the risk for the progression of fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), contributing to increased morbidity and mortality (2). The number of patients with CHB ranges from 240 million to 350 million (3). The prevalence of CHB varies worldwide, with the highest prevalence in western sub-Saharan Africa (12%), followed by East Asia and Southeast Asia (5%-7%) (1,2,3,4,5). In our country, the prevalence of hepatitis B surface antigen (HBsAg) positivity varies between 4% and 10%, and it is considered to be a moderately endemic region in terms of HBV incidence (6).

Hepatosteatosis is the most common cause of elevated liver enzyme levels worldwide and is defined as the accumulation of lipid droplets in hepatocytes (7). It is frequently associated with metabolic factors, including central obesity, insulin resistance, and hypertriglyceridemia (8). The prevalence of hepatosteatosis is increasing due to the increasing prevalence of obesity and/or metabolic syndrome worldwide (9). Since liver fibrosis is a shared pathological process in patients with chronic viral hepatitis (CVH) and hepatosteatosis, recent studies have been conducted to evaluate the interaction between HBV, hepatitis C virus (HCV), and hepatosteatosis (10).

Hepatosteatosis is a common histopathological feature of chronic hepatitis C (CHC) infection and has been shown to be particularly associated with genotype 3 (11). Although controversial, the presence of hepatosteatosis in patients with CHC has been associated with advanced fibrosis (12,13). However, the relationship between HBV and hepatosteatosis has not been explained. The aim of this study was to investigate the frequency of ultrasonography (USG) defined hepatosteatosis in patients with CHB and the relationship between the presence and severity of hepatosteatosis and biochemical, virological, and metabolic parameters.

Materials and Methods

Patient Population

We retrospectively studied all patients with CHB who were admitted to the infectious diseases and clinical microbiology outpatient clinic between January 2022 and June 2022.

The inclusion criteria considered were the following: HBsAg positivity for a period over 6 months. Exclusion criteria were as follows: co-infection with other viruses such as HCV, HDV, and human immunodeficiency virus (HIV), co-existence of liver disease of any other cause, consumption of alcohol more than 30 g/day for males or 20 g/day for females, obese patients body mass index (BMI) >30, diagnosis of dyslipidemia, and treatment with tenofovir alafenamide fumarate.

Patients were divided into two groups, hepatosteatosis and non-hepatosteatosis, according to liver USG findings. The groups were evaluated in terms of variables such as age, gender, liver enzymes, Hepatitis B e antigen (HBeAg) status, HBV-DNA level, hepatitis B infection stage (chronic infection, chronic hepatitis), antiviral treatment status, BMI, glucose, triglyceride, and cholesterol levels.

Statistical Analysis

The distribution of the data was analyzed by the Kolmogorov-Smirnov test, and group comparisons were made by the Independent samples t-test for continuous variables with normal distribution and the Mann-Whitney U test for continuous variables without normal distribution. Relationships between categorical variables were analyzed using Pearson's chi-square or Fisher's exact tests.

Categorical variables are shown as n (%). Continuous variables with normal distribution are shown as mean ± standard deviation, while the median (interquartile range) (minimum-maximum) was used for continuous variables that did not show normal distribution. Statistical analyses were performed using SPSS v.22 Package program, and the significance level was set at 0.05. Before starting the study, the approval of the Scientific Research Ethics Committee of the Faculty of Medicine of Ağrı İbrahim Çeçen University was obtained (approval number: 229, date: 08.11.2022).

Results

A total of 262 patients with CHB were included in the study. The mean age was 45.1±15.3 years. There were 136 males (51.8%) and 126 females (48.2%). The majority of patients were HbeAg negative 238/262 (90.8%), whereas only 24/262 were HbeAg-positive (19.2%). A liver biopsy was performed in 86 patients (32.8%), whereas 20 patients (7.6%) had fibrosis. In addition, 163 (62.2%) patients had steatosis and 99 (37.8%) did not have steatosis. Among the patients with hepatosteatosis grade

1, steatosis was observed in 30.9% (81/163), grade 2 in 26% (68/163), and grade 3 in 5.3% (14/163).

Hypertension (HT), hepatomegaly, and cirrhosis were correlated with the presence of steatosis. Patients with steatosis were older than those without steatosis (48.36±14.92 versus 39.82±14.52 years, p<0.001). Fasting blood glucose (97.42±17.5 mg/dL versus 93.09±13.94 mg/dL, p=0.040), low-density lipoprotein (LDL) levels (105.57±25.82 mg/dL versus 98.65±24.33 mg/dL, p=0.032) and triglyceride levels (114.57±25.82 mg/dL versus 98.65±24.33 mg/dL, p=0.003) of patients with steatosis were higher than those without steatosis. HDL levels were lower in the steatosis Grup (47.24±13.26 mg/dL versus 43.22±10.42 mg/dL, p=0.007). No correlation was found between gender, BMI, HDV coinfection, HBV-DNA levels, and HBeAg status between steatosis (Table 1).

Liver biopsy was performed on 102 patients, but biopsy results were available for 86 of them. Hepatosteatosis was detected in 30 (34.8%) patients. When the patients who had liver biopsy were divided into two groups, those with and without steatosis, according to the biopsy results, it was found that older age, presence of cirrhosis, high LDL, triglycerides, and low HDL were associated with steatosis, but HT was not found to be statistically significant, whereas HBV-DNA levels were found to be higher in the group with steatosis, and this difference was statistically significant (Table 2).

Table 1. Comparative analysis of clinical and biochemical parameters in chronic hbv patients with and without hepatosteatosis

	With steatosis (n=99)	**Without steatosis (n=163)**	**p-value**
Age (year)	39.82±14.52	48.36±14.92	<0.001*
BMI (kg/m²)	24.67±2.67	24.85±2.99	0.624*
Gender, n (%) Female Male	 54 (54.5) 45 (45.5)	 72 (44.2) 91 (55.8)	0.103#
BMI >25, n (%)	36 (36.4)	58 (35.6)	0.898#
DM, n (%)	1 (1.0)	2 (1.2)	>0.999$
HT, n (%)	4 (4.0)	18 (11.0)	0.048$
Cirrhosis, n (%)	0 (0.0)	19 (11.7)	<0.001$
HDV, n (%)	3 (3.0)	7 (4.3)	0.747$
HBe, n (%) AntiHBe positive HBeAg positive	 88 (88.9) 11 (11.1)	 150 (92.0) 13 (8.0)	0.394#
Liver inflammation, n (%) Infection Hepatitis	 37 (37.4) 62 (62.6)	 61 (37.4) 102 (62.6)	0.994#
Age of the disease	6 (7) [1-23]	8 (5) [0-33]	0.151&
Fasting glucose (mg/dL)	93.09±13.94	97.42±17.75	0.040*
ALT (U/L)	23.99±14.00	25.54±13.44	0.373*
AST (U/L)	22.72±7.49	23.83±9.57	0.325*
Cholesterol (mg/dL)	163.69±41.88	168.05±38.24	0.389*
TG (mg/dL)	97 (59) [38-683]	114 (65) [29-417]	0.003&
HDL (mg/dL)	47.24±13.26	43.22±10.42	0.007*
LDL (mg/dL)	98.65±24.33	105.57±25.82	0.032*
AFP (ng/mL)	2 (1) [1-11]	2 (2) [1-13]	0.109&
HBV-DNA (IU/mL)	569 (944) [60-8590]	612 (1464) [90-9890]	0.635&
Hepatomegaly, n (%)	6 (6.1)	55 (33.7)	<0.001#
Treatment, n (%) TDF ETV	40 (40.4) 23 (57.5) 17 (42.5)	73 (44.8) 40 (54.8) 33 (45.2)	0.488# 0.782#
Liver biopsy, n (%)	39 (39.4)	63 (38.7)	0.905#
HAI (n=30 vs. 56)	7 (3) [3-13]	8 (3) [2-12]	0.599&
Fibrosis (n=30 vs. 56)	2 (1) [1-6]	2 (1) [0-5]	0.694&

*: Independent samples t-test, #: Pearson chi-square test, $: Fisher's exact, &: Mann-Whitney U test, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, HDV: Hepatitis delta virus, HBeAg: Hepatitis B envelope antigen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TG: Triglyceride, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AFP: Alfa fetoprotein, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, TDF: Tenofovir disoproxil fumarate, ETV: Enticavir, HAI: Histological activity index

Discussion

Hepatosteatosis and CVH are both common chronic liver diseases worldwide (14,15,16). It is commonly associated with metabolic risk factors such as obesity, dyslipidemia, and insulin resistance (17). The estimated global prevalence of hepatosteatosis is 25% (18). The prevalence of hepatosteatosis in Turkey has been studied in several small-sized, single-center studies and was found to vary between 10% and 48% (19,20,21,22). The highest hepatosteatosis rate of 60.1% was reported from the Cappadocia cohort, an ultrasound-based study of 2792 apparently healthy individuals (60.1%) (23). Current studies show that Turkey is among the countries with a high prevalence of hepatosteatosis in the world (19,20,21,22,23).

HBV and HCV infection leads to a spectrum of liver diseases, including chronic hepatitis, cirrhosis, and HCC (24). Studies evaluating steatosis in patients with CHC have shown a direct relationship between HCV and steatosis (10). However, this is a feature-specific to genotype 3. In patients infected with genotype 3, fatty liver disease is directly proportional to viral load, and steatosis starts in the periportal area, not in the centrilobular area, unlike patients with hepatosteatosis (12,13). Fatty liver disease in patients infected with other HCV genotypes is associated with obesity, Diabetes Mellitus, and insulin resistance, as in other patients with hepatosteatosis.

It has been reported that hepatosteatosis is associated with 14-70% of patients with CHB (25,26,27). This rate is approximately 20% in biopsy-proven hepatosteatosis (26). In our study, the hepatosteatosis rate was found to be 63% in patients with CHB. Although this rate is similar to other studies evaluating hepatosteatosis in patients with CHB, it is higher than that in the normal population. The high prevalence of hepatosteatosis suggested that it may be related to CHB, but no statistical association was found. This might be because the diagnosis of hepatosteatosis is made by USG, not biopsy, because when the patients were compared with and without steatosis according to biopsy results, HBV-DNA levels were found to be higher in the group with steatosis, and this difference was statistically significant.

Table 2: Detailed characteristics of chronic hepatitis B virus patients with and without hepatosteatosis undergoing liver biopsy

	Without steatosis (n=39)	**With steatosis (n=63)**	**p-value**
Age (year)	43.15±13.23	50.30±13.93	0.012*
BMI (kg/m²)	24.46±2.78	25.24±3.47	0.240*
Gender n (%) Female Male	 19 (48.7) 20 (51.3)	 28 (44.4) 35 (55.6)	0.674
BMI >25, n (%)	15 (38.5)	25 (39.7)	0.902#
DM, n (%)	1 (2.6)	0 (0.0)	0.382$
HT, n (%)	3 (7.7)	11 (17.5)	0.164$
Cirrhosis, n (%)	0 (0.0)	11 (17.5)	0.006$
HDV, n (%)	1 (2.6)	5 (7.9)	0.403$
HBeAg, n (%) AntiHBe positive HBeAg positive	 33 (84.6) 6 (15.4)	 55 (87.3) 8 (12.7)	0.702#
Age of the disease	7 (7) [1-23]	8 (4) [1-23]	0.159&
Fasting glucose (mg/dL)	94.03±9.48	100.57±20.01	0.029*
ALT (U/L)	23.10±10.75	26.81±12.69	0.132*
AST (U/L)	23.62±8.56	25.59±11.51	0.358*
Cholesterol (mg/dL)	170.28±38.54	166.35±33.99	0.591*
TG (mg/dL)	96 (62) [40-240]	114 (57) [54-260]	0.007&
HDL (mg/dL)	48.74±15.56	41.65±9.26	0.013*
LDL (mg/dL)	103.87±26.28	105.02±24.48	0.824*
AFP (ng/mL)	2 (1) [1-11]	2 (1) [1-13]	0.716&
HBV-DNA	1278 (1958) [124-8590]	2096 (3262) [138-9890]	0,039&
Hepatomegaly, n (%)	1 (2.6)	21 (33.3)	<0.001$
Treatment, n (%) TDF ETV	33 (84.6) 19 (57.6) 14 (42.4)	60 (95.2) 34 (56.7) 26 (43.3)	0.082# 0.932#

*: Independent samples t-test, #: Pearson chi-square test, $: Fisher's exact, &: Mann-Whitney U test, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, HDV: Hepatitis delta virus, HBeAg: Hepatitis B envelope antigen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TG: Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, AFP: Alfa fetoprotein, HBV-DNA: Hepatitis B virus deoxyribonucleic acid, TDF: Tenofovir disoproxil fumarate, ETV: Enticavir

There has been an increase in the number of cases in which CHB and hepatosteatosis are observed together. In the study evaluating 132 CHB patients who underwent liver biopsy, it was shown that the presence of steatosis was not associated with age, gender, HBeAg status, HBV-DNA level, presence of fibrosis, serum cholesterol level, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. In univariate analysis, BMI, serum triglyceride, and fasting glucose levels were significantly correlated with hepatosteatosis. Multivariate analysis showed a correlation only between serum triglyceride level and hepatosteatosis (25). In another study, steatosis was independently found to be associated with fasting glucose level and BMI ≥25, no correlation between HBV-DNA levels and HBeAg status (28). In our study, similar to these studies, HT, hepatomegaly, and cirrhosis were correlated with the presence of steatosis. However, no correlation was found with HBV-DNA levels or HBeAg status (26).

In a meta-analysis and a study examining the risk factors for hepatosteatosis in HBV-infected patients, it was shown that hepatosteatosis may have a protective effect on CHB by reducing HBV viral markers (28). The lower incidence of cirrhosis and HCC in HBV-infected patients with hepatosteatosis is associated with higher HBsAg clearance (29). In another study evaluating the effect of HBV on steatosis in people co-infected with HCV, only BMI, not viral factors, was associated with the development of non-alcoholic fatty liver disease (NAFLD) in CHB patients. In the co-infected study population, only BMI and fasting plasma glucose levels were associated with NAFLD. In subgroup analysis, even in patients with genotype 3, CHC and CHB together showed less steatosis than patients with genotype 3 CHC alone (30). This suggests that there is an underlying mechanism in CHB infection that is protective against the development of NAFLD. In our study, we did not show a correlation of steatosis with HBV parameters when the patients were compared with and without steatosis according to liver USG findings results. However, HBV-DNA levels were found to be higher in the group with steatosis, and this difference was statistically significant when the patients who had biopsy were divided into two groups as with and without steatosis. This situation suggests that further studies are needed to evaluate the relationship between HBV and fatty liver disease defined by biopsy in many patients.

Study Limitation

The most important limitation of our study is that the diagnosis of steatosis was made by USG, not biopsy. Liver biopsy is probably the most reliable method for detecting fatty liver (33). However, liver biopsy is not a routine method for diagnosing hepatosteatosis in clinical practice because it is an invasive and costly procedure that may cause morbidity and mortality (17). Diagnosis of hepatosteatosis by USG is a subjective evaluation based on the radiologist's knowledge and visual perception (especially, grade 1 hepatosteatosis). Therefore, we believe that if hepatosteatosis rates were determined by biopsy in our study, a slightly lower rate might be obtained.

Conclusion

In conclusion, we found that hepatosteatosis is present in a significant proportion of patients with CHB. The presence of steatosis is associated with metabolic parameters such as elevated CVH, triglyceride levels, and fasting glucose levels. This study did not show a correlation of steatosis with HBV parameters, but additional well-designed studies are required to prospectively assess the role of steatosis in these patients.

Ethics

Ethics Committee Approval: The approval of the Scientific Research Ethics Committee of the Faculty of Medicine of Ağrı İbrahim Çeçen University was obtained (approval number: 229, date: 08.11.2022).

Informed Consent: Retrospectively study.

Authorship Contributions

Surgical and Medical Practices: Y.Ç., M.Ö., Concept: Y.Ç., S.A.B., Design: Y.Ç., M.A.S., Data Collection or Processing: Y.Ç., M.A.S., M.Ö., Analysis or Interpretation: Y.Ç., M.A.S., Literature Search: Y.Ç., M.Ö., S.A.B., Writing: Y.Ç., S.A.B.

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