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Effect of hepatic steatosis on virological response to nucleos(t)ide analogs therapy in patients with chronic hepatitis B

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Aim: To evaluate the impact of hepatic steatosis on the outcome of treatment in patients with chronic hepatitis B infection treated with oral antiviral therapy.

Materials and methods: The study was designed in Erciyes University Medical Faculty Department of Gastroenterology. Patients who received oral antiviral therapy because of chronic hepatitis B were included in the study. Liver biopsy specimens were re-evaluated and classified according to Brunt's steatosis classification. Virological response to oral antiviral therapy was compared between patients with and without steatosis.

Results: One hundred and nineteen patients were included in the study, of which 36.1% had hepatic steatosis. Virological response rates were 81% and 85.5% in patients with steatosis and without steatosis, respectively. There was no statistically significant difference in virological response rate between patients with and without steatosis (p: 0.78). Median hepatic fibrosis values were 3 and 2 in patients with steatosis and without steatosis respectively (p: 0.01).

Conclusion: Many studies have researched the prevalence and effect of steatosis on the liver in chronic hepatitis B. Although steatosis does not affect the outcome of treatment, it is not a rare condition in chronic hepatitis B.

Key words: Hepatic steatosis, hepatitis B, viral response, antiviral therapy, nucleos(t)ide analogs, liver fibrosis

1. Introduction

Lipid accumulation in the liver, so-called hepatic steatosis or nonalcoholic fatty liver disease (NAFLD), is a common condition frequently found in subjects who are not affected by any other liver disease and who do not drink alcohol; it affects 10%–24% of the population (1). Hepatic steatosis prevalence has been estimated by magnetic resonance studies to be 35% in the general population and to be 75% in obese persons, and these figures seem to be continually increasing (2–4). In fact, in only 2% of the general population does hepatic steatosis constitute a real hepatic disease: nonalcoholic steatohepatitis (NASH) with deranged aminotransferases and fibrosis.

Hepatitis B virus (HBV) infection continues to be a major health problem worldwide. It is estimated that there are over 400 million chronic carriers of HBV (5). One study reported that the seroprevalence of hepatitis B is 2.2% in Turkey (6). There is a high prevalence of hepatitis B in blood donors in some countries (7). Chronically infected individuals have a higher risk of death from cirrhosis and liver cancer. It is well known that hepatic steatosis is reported to share common histological features with chronic hepatitis C (CHC), and is associated with metabolic and viral factors. Hepatic steatosis may affect the severity of fibrosis in CHC (8). The prevalence and clinical significance of steatosis in patients with chronic hepatitis B (CHB) are poorly understood. We suggest that there is a relationship between response to CHB treatment and hepatic steatosis. Only a small number of studies on this subject have been published and some of these reported the prevalence of steatosis in CHB (9,10). The presence of steatosis correlates with body mass index (BMI), waist circumference, high blood pressure, and dyslipidemia, but not with viral genotype or viral load. Moreover, steatosis does not correlate with fibrosis (8).

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Nucleos(t)ide analogs (NUCs) are an approved treatment for CHB. HBeAg, ALT, and HBV DNA measurements could be of significant help in the selection of hepatitis B patients who would benefit from antiviral treatment. HbeAg seroconversion and undetectable HBV DNA level are associated with increased survival in patients with CHB (11). However, the impact of hepatic steatosis on the response rate to antiviral treatment, especially with NUCs, has not been studied in CHB. The aim of this retrospective study was to determine the prevalence of hepatic steatosis in CHB and the impact of hepatic steatosis on the outcome of treatment in patients with CHB treated with NUCs.

2. Materials and methods

This study was approved by the Ethics Committee of Erciyes University Faculty of Medicine. The patients who were treated and monitored for CHB infection at the Department of Gastroenterology at Erciyes University from 2005 to 2010 were reached via patient follow-up cards and computer-based patient records. Patients who had already received NUCs or had previously been treated with these drugs for at least 48 weeks for CHB infection were included in the study. Patients who had concurrent CHC and chronic hepatitis D infection, any chronic liver disorders, chronic alcohol dependence, had previously been treated with interferon, and those with cirrhosis were excluded. Diagnosis of CHB infection was made from a liver biopsy showing findings for CHB; a biopsy was performed after the determination of HBsAg, detection of HBV DNA, or elevated ALT levels measured in 2 separate samples taken at least 6 months apart. The demographical data of the patients were recorded and used for statistical analyses.

2.1. Histological evaluation

The pathology samples of patients were reviewed retrospectively and re-assessed by an experienced pathologist in the pathology laboratory. The slides were stained with hematoxylin–eosin, silver, and trichrome stains and were evaluated under a light microscope (Olympus, BX51, Japan) according to the modified Ishak system (12). Hepatic steatosis was scored according to Brunt's classification (13).

2.2. Treatment protocols and evaluation of the response to treatment

Virological response to NUCs was defined as undetectable HBV DNA by real-time PCR assay within 48 weeks of therapy. The rate of viral response to NUCs was assessed independently from the steatosis. The liver biopsies of patients who had received NUCs (lamivudine, entecavir, or tenofovir) for at least 48 weeks were grouped according to Brunt's classification as grade 0, 1, 2, or 3 steatosis. They were also evaluated in 2 groups as those with and without steatosis.

2.3. Statistical analysis

Data were initially assessed for normality and log-transformed where appropriate. Baseline descriptive data were expressed as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. A Shapiro–Wilk test was used to assess the normal distribution of data. The analysis of qualitative variables was assessed using a chi-square test. To compare numerical values Student's t-test was used if the data had a normal distribution while a Mann–Whitney U test was used if the data did not. For all comparisons, statistical significance was determined at the 0.05 level.

3. Results

One hundred and nineteen patients were included in the study, of whom 76 (63.8%) were male and 43 (36.2%) female. The mean age, basal ALT levels, basal HBV-DNA levels, HAI scores, fibrosis scores, BMI, total cholesterol, and fasting triglyceride levels of groups with and without steatosis are shown in Table 1. There were statistically significant differences in BMI, total cholesterol, and fasting triglyceride levels between the groups (Table 1). Apart from hepatic steatosis, 100 (84.1%) of the 119 patients had a virological response at week 48, whilst 19 patients (15.9%) had no or a partial virological response. When the rates of treatment responses were compared according to sex and age, no statistically significant difference was found (Table 2).

Seventy-eight (63.9%) of the 119 patients had no steatosis, 36 (30.3%) had grade 1 steatosis, and 7 (5.9%) had grade 2 steatosis. No statistically significant difference in virological response was found between the groups (Table 3).

4. Discussion

Hepatic steatosis may occur as a common histopathological sign of several liver disorders unrelated to each other in terms of causes, pathogenesis, and clinical courses. The clinical course may be ingenuous or may result in cirrhosis, leading to severe necroinflammation and fibrosis, causing significant risks of liver-related morbidity and mortality. Hepatic steatosis is a metabolic disease that makes the liver more vulnerable to harmful agents and leads to accumulation of fatty tissue within the liver. Therefore, it is expected that patients with hepatic steatosis will have a poorer response to antiviral treatment. It is known that hepatic steatosis has a negative effect on treatment responses in CHC infection. It was reported that HCV core protein played an important role in the development of steatosis in CHC infection. It was proposed that HCV caused viral steatosis in addition to metabolic steatosis (14). That argument may explain why steatosis is more common in CHC when compared with CHB.

Table 1. Comparisons of patients with and without steatosis.

Parameter	Whole group (n = 119)	With steatosis (n = 43 36.1%)	Without steatosis (n = 76 63.9%)	P
Age (years)	41.3 ± 13.7	43.8 ± 11.7	40.03 ± 13.8	>0.05
Age of males	42 ± 13.9	41.9 ± 14.04	42.2 ± 13.89	0.9
Age of females	40.1 ± 13.57	43.7 ± 13.19	35.9 ± 13.03	**0.029**
Median value of basal ALT (IU/L)	85	74.5	93.0	0.17
Median value of HAI	5	5	4	0.18
Median value of fibrosis	3	3	2	**0.01**
Basal HBV-DNA (IU/mL)	1.2×10^7	9.9×10^6	1.3×10^7	0.451
BMI (kg/m^2)	26 ± 4	29 ± 5	25 ± 4	**0.001**
Total cholesterol (mg/dL)	209 ± 72	260 ± 62	180 ± 60	**0.001**
Triglyceride (mg/dL)	202 ± 55	240 ± 52	182 ± 58	**0.001**

Table 2. Comparison of patients according to virological response.

Parameter	Patients having virological response to treatment n (%)	Patients not having virological response to treatment n (%)	P
Men	65 (86)	11 (14)	0.63
Women	35 (82)	8 (18)	
General	100 (84.1)	19 (15.9)	0.076
Age	42.4 ± 13	36.7 ± 16.2	0.16
With steatosis	35/43 (81)	8/43 (19)	0.78
Without steatosis	65/76 (85.5)	11/76 (14.5)	

Table 3. Distribution of hepatic steatosis and virological response.

Grading of steatosis	Number (%)	Virological response %
None	76 (63.9)	85.5
Grade 1	36 (30.3)	81.8
Grade 2	7 (5.9)	83.3
Grade 3	0	-
Total	119	84.8

No statistically significant difference between groups.

There is an insufficient number of studies relevant to the natural course and treatment response rates of patients with CHB infection and hepatic steatosis. The prevalence of hepatic steatosis was 42.4% and hepatic steatosis was only correlated with serum triglyceride level in patients with CHB in a study from Iran (15). In contrast, Shi et al. reported that steatosis was independent of factors such as BMI, serum triglyceride and apoprotein levels, uric acid, and fasting plasma glucose in patients with CHB (16). The prevalence of hepatic steatosis was 33.4% in a study reported by Mi et al. (17). In that study, BMI, fasting blood glucose, serum triglyceride, and the total cholesterol levels of patients with steatosis were significantly higher than those of patients without steatosis (17). Shi et al. evaluated 562 patients with CHB infection and found that the rate of hepatic steatosis was 18.15%. The results obtained from patients with steatosis were similar to the data of the studies mentioned above (18). In a study conducted in Tunisia, Elloumi et al. reported a hepatic steatosis rate of 34.1% in patients with CHB and the authors reported that only BMI and serum cholesterol levels were influential factors in the development of hepatic steatosis in the patients with CHB (19). As seen in these studies, the rates of steatosis varied widely. This variability may result from different ethnicity, certain metabolic properties of the population included in the study, and even from individual differences during histopathological evaluations.

When the literature was reviewed, it was seen that the data regarding the effect of hepatic steatosis on treatment were rather limited in CHB. Cindoruk et al. conducted a study to ascertain if hepatic steatosis affects response to treatment in patients receiving interferon for CHB infection. In that study, the prevalence of hepatic steatosis was 34.2% and it was concluded that hepatic steatosis did not affect treatment response (20). In our study, although hepatic steatosis was observed at a rate of 36.1% in patients with CHB, it did not impact virological response.

The association between steatosis and fibrosis is a common observation in NASH. Because of this fact we did not include patients with NASH in the study. While Peng et al. reported that steatosis was not related to fibrosis (9), we found a statistically significant correlation between steatosis and hepatic fibrosis; the more steatosis increases, the more fibrosis develops. The observation that fibrosis is significantly higher in patients with steatosis is not new, and, in any case, the relationships between steatosis and fibrosis have been evaluated in different studies (20,21). Considering that the main cause of morbidity and mortality due to hepatitis B infection is related to the development of hepatic fibrosis, this is an important finding. It is well known that hepatic steatosis resulting from any cause leads to oxidative stress and mitochondrial dysfunction and consequent inflammatory changes and fibrosis (22,23). In CHC infection, increased fibrosis due to steatosis is related to many pathways such as oxidative stress, increased vulnerability to apoptosis, and impaired response to cellular damage. Similar pathways may also take place in CHB infection with hepatic steatosis; further studies on this subject are needed.

Although the rates of VR in patients with hepatic steatosis treated with NUCs were lower in comparison with those without hepatic steatosis who received the same treatment, there was no significant difference between the groups. This situation may be related to the low severity of the steatosis present in the patients with steatosis in this study.

Our study had certain limitations (lack of some parameters such as insulin resistance) since it was a retrospective study. Another limitation was that genotypes were not known; however, most patients with CHB in Turkey have genotype D. Considering this information and studies reporting that the outcomes of treatments with oral antiviral drugs are independent of the HBV genotype, it is thought that these limitations may not have significantly affected the results of the study (23).

In conclusion, hepatic steatosis is not rare in patients with CHB but it does not affect the virological response to oral antiviral treatment in these patients.

References

1. Angulo P, Lindor KD. Non-alcoholic fatty liver disease. Journal of Gastroenterology and Hepatology 2002; 17 Suppl: S186–90.
2. Czaja AJ, Carpenter HA. Sensitivity, specificity, and predictability of biopsy interpretations in chronic hepatitis. Gastroenterology 1993; 105: 1824–32.
3. Bellentani S, Saccoccio G, Masutti F, Crocè LS, Brandi G, Sasso F et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000; 132: 112–7.
4. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004; 40: 1387–95.
5. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004; 11: 97–107.
6. Oner S, Yapıcı G, Şaşmaz CT, Kurt AO, Buğdaycı R. Hepatitis B, hepatitis C, HIV, and VDRL seroprevalence of blood donors in Mersin, Turkey. Turk J Med Sci 2011; 41: 335–341.

7. Nwankwo E, Momodu I, Umar I, Musa B, Adeleke S. Seroprevalence of major blood-borne infections among blood donors in Kano, Nigeria. Turk J Med Sci 2012; 42: 337–341.

8. Asselah T, Rubbia-Brandt L, Marcellin P, Negro F. Steatosis in chronic hepatitis C: why does it really matter? Gut 2006; 55: 123–30.

9. Peng D, Han Y, Ding H, Wei L. Hepatic steatosis in chronic hepatitis B patients is associated with metabolic factors more than viral factors. Journal of Gastroenterology and Hepatology 2008; 23: 1082–8.

10. Bondini S, Kallman J, Wheeler A, Prakash S, Gramlich T, Jondle DM et al. Impact of non-alcoholic fatty liver disease on chronic hepatitis B. Liver Int 2007; 27: 607–11.

11. Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. N Engl J Med 1996; 334: 1422–7.

12. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981; 1: 431–5.

13. Brunt EM, Janney CG, Di Biseeglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. The American Journal of Gastroenterology 1999; 94: 2467–74.

14. Leandro G, Mangia A, Hui J, Fabris P, Rubbia-Brandt L, Colloredo G et al. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. Gastroenterology 2006; 130: 1636–42.

15. Minakari M, Molaei M, Shalmani HM, Alizadeh AH, Jazi AH, Naderi N et al. Liver steatosis in patients with chronic hepatitis B infection: host and viral risk factors. European Journal of Gastroenterology & Hepatology 2009; 21: 512–6.

16. Shi JP, Fan JG, Wu R, Gao XQ, Zhang L, Wang H et al. Prevalence and risk factors of hepatic steatosis and its impact on liver injury in Chinese patients with chronic hepatitis B infection. Journal of Gastroenterology and Hepatology 2008; 23: 1419–25.

17. Mi YQ, Liu YG, Xu L, Fan JG, Zhang H, Ping L et al. [Analysis of clinical and pathological features of chronic hepatitis B with hepatic steatosis]. Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chinese Journal of Hepatology, 2009; 17: 817–20.

18. Shi JP, Fan JG, Wu R, Gao XQ, Zhang L. [Viral and host causes of hepatosteatosis in Chinese patients with chronic hepatitis B]. Zhonghua shi yan he lin chuang bing du xue za zhi = Zhonghua shiyan he linchuang bingduxue zazhi = Chinese Journal of Experimental and Clinical Virology, 2008; 22: 324–6.

19. Cindoruk M, Karakan T, Unal S. Hepatic steatosis has no impact on the outcome of treatment in patients with chronic hepatitis B infection. Journal of Clinical Gastroenterology 2007; 41: 513–7.

20. Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. J Gastroenterol Hepatol 2011; 26: 1361–7.

21. Petta S, Cammà C, Di Marco V, Macaluso FS, Maida M, Pizzolanti G 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: 507–15.

22. Berson A, De Beco V, Lettéron P, Robin MA, Moreau C, El Kahwaji J et al. Steatohepatitis-inducing drugs cause mitochondrial dysfunction and lipid peroxidation in rat hepatocytes. Gastroenterology 1998; 114: 764–74.

23. EASL Clinical Practice Guidelines: management of chronic hepatitis B. Journal of Hepatology 2009; 50: 227–42.