Impact of liver steatosis on response to pegylated interferon therapy in patients with chronic hepatitis B

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Abstract

AIM: To evaluate the impact of liver steatosis upon response to given therapy in chronic hepatitis B (CHB) patients.

METHODS: 84 consecutive CHB patients treated with 48-wk PEGylated interferon (PEG-IFN) therapy were enrolled. Baseline characteristics and sustained viral response (SVR) to PEG-IFN therapy were evaluated.

RESULTS: Mean body mass index (BMI) was 27.36 ± 4.4 kg/m². Six (7.1%) had hypertension and three (3.5%) had diabetes mellitus. Steatosis was present in 22.6% (19/84) of liver biopsy samples. Age, BMI, and triglyceride levels of the patients with hepatic steatosis were significantly higher than those without hepatic steatosis (P < 0.05). SVR to PEG-IFN therapy was 21.4% (18/84). Sixteen of these 18 CHB patients with SVR (88.9%) did not have any histopathologically determined steatosis. On the other hand, only two of the 19 CHB patients with hepatic steatosis had SVR (10.5%). Although the SVR rate observed in patients without steatosis (16/65, 24.6%) was higher compared to those with steatosis (2/19, 10.5%), the difference was not statistically significant (P > 0.05).

CONCLUSION: Occurrence of hepatic steatosis is significantly high in CHB patients and this association leads to a trend of decreased, but statistically insignificant, SVR rates to PEG-IFN treatment.

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Key words: Chronic hepatitis B; Hepatic steatosis; Pegylated interferon therapy

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INTRODUCTION

Fatty livers, defined by the accumulation of lipid droplets, mainly triglycerides, in hepatocytes, are vulnerable to factors associated with further hepatic injury by their increased sensitivity to oxidative stress and to cytokine-mediated hepatic damage. This alone may not only lead to chronic liver disease, but can also influence the progression of chronic liver diseases with different etiologies and the response to given therapy. Steatosis, together with obesity and type 2 diabetes mellitus (DM), is also a proposed risk factor for the development of hepatocellular carcinoma[1].

Steatosis has been observed in the majority of chronic alcoholics and is also a common histopathological feature of chronic hepatitis C (CHC) infection. In patients with CHC, steatosis of the liver, accompanied by metabolic...
and viral factors, increases the severity of fibrosis and unfavorably influences the response to given therapy. Steatosis, however, may co-exist with other chronic liver diseases, in addition to alcoholic liver diseases and hepatitis C, because of the increasing prevalence of obesity and metabolic syndrome.

The number of studies reporting co-existence of steatosis and chronic hepatitis B (CHB), a major cause of chronic liver disease worldwide, is increasing. The impact of superimposed non-alcoholic fatty liver disease in patients with CHB, however, is less clear. There are only a few studies on this topic. The components of metabolic syndrome [obesity, hypertension (HTA), and dyslipidemia] are associated with the presence of nonalcoholic steatohepatitis in patients with CHB, and the presence of hepatic fibrosis seems to be associated with known host and viral factors, as well as the presence of abdominal obesity.

We aimed to determine the frequency and risk factors of liver steatosis in patients with CHB, and to investigate its correlation with the response to given PEGylated interferon (PEG-IFN) therapy.

MATERIALS AND METHODS

Patients
Twenty-one hepatitis B e antigen (HBeAg) (+) and 63 HBeAg (-) (n = 84) consecutive patients with CHB, who were diagnosed by liver biopsy, and received 48-wk PEG-IFN therapy were enrolled in the study between December 2006 and July 2009. Patients were given either PEG-IFN α-2a or 2b. Forty patients received PEG-IFN α-2a 180 μg sc and 44 patients received Peg-IFN α-2b 1.5 μg/kg sc once a week. Sixty of the patients were male (71.4%) and 24 were (28.6%) female, their mean age was 38.6 ± 10.9 years and their age range was 18-61 years.

Before inclusion, the patients were informed and their written consents were obtained. The study protocol was approved by the local Ethics Committee, and the study was performed in accordance with the ethical standards laid down in an appropriate version of the 1975 Declaration of Helsinki.

Inclusion criteria
In the serum samples of the patients enrolled to the study, the hepatitis B surface antigen (HBsAg) had to have been present for more than 6 mo and, within the last 6 mo, at least two different measurements must have shown an elevation of alanine aminotransferase (ALT) > ULN × 2. The liver biopsies of all patients were consistent with the diagnosis of CHB.

Exclusion criteria
Patients who met at least one of the following were excluded from the study: patients co-infected with other viruses, such as hepatitis A, C, D, E, Cytomegalovirus, Epstein-Barr virus and HIV; patients with toxic hepatitis; patients with another liver disease; alcohol consumers (more than 20 g per day); patients who were taking antiviral drugs or interferon before the biopsy.

Body mass index (BMI) was calculated by dividing the body weight (kg) by the square of height (m). Based on the BMI values, < 25 kg/m² was considered as normal, 25-30 kg/m² as overweight, and > 30 kg/m² as obese.

Serum analyses
Fasting blood samples were obtained 1 d before the liver biopsy, and ALT, aspartate aminotransferase, \( \gamma \) glutamyltransferase, glucose (GLU), cholesterol, and triglyceride levels were measured.

Virological analyses
For the analyses, HBsAg, HBeAg, Anti-HBe, Anti-HBc ARCHITECT chemiluminescent microparticle immunosay kits (Abbott Park, Wiesbaden-Delkenheim, Germany) and ARCHITECT i2000 system were used. HBV DNA levels were studied quantitatively using an HBV RG PCR Kit (sensitivity: 100 copies/mL) and Rotor-Gene 3000 (Corbett Research) device. Sustained viral response (SVR) was defined as the fall in HBV DNA to undetectable levels (< 100 copies/mL) 6 mo after (week 72) the end of 1-year PEG-IFN α therapy and disappearance of HBeAg in cases with HBeAg (+).

Histological evaluation
All percutaneous liver biopsies were performed by two experienced gastroenterologists using a 16-gauge needle. All histological analyses were performed by one experienced pathologist who was blinded to the study. Necroinflammation was determined by scoring according to Knodell's histological activity index (HAI): portal inflammation (0-4), lobular degeneration and focal necrosis (0-4), pericentral ± bridging necrosis (0-10). The stage of fibrosis was classified from “no fibrosis” (Stage 0) to cirrhosis (Stage 4). Grading of hepatosteatosis was semiquantitatively performed according to hepatocyte involvement: None:0, Mild: 0%-10%, Moderate:10%-30%, Marked: 30%-60%, and Severe: > 60%.

Statistical analysis
While the numerical data of the patients were presented as mean ± SD, categorical variables were presented together with frequency and percentages. The intergroup differences of numerical variables were investigated using Student’s t test, while the differences of categorical values were investigated using the \( \chi^2 \) test. Variables that were found to be significant in univariate analysis (\( P < 0.05 \)) were subjected to a multivariate logistic regression model to be investigated. All analyses were performed using a statistical software program (SPSS version 15.0).

RESULTS

Patient characteristics
Among 84 patients enrolled to the study, six (7.1%) had HTA and three (3.5%) had DM. The mean BMI value was...
27.36 ± 4.4 kg/m². When the patients were evaluated according to their BMI, 28 (33.3%) were grouped as normal (< 25 kg/m²), 34 (40.5%) as overweight (25-30 kg/m²), and 22 (26.2%) as obese (> 30 kg/m²). The demographic, clinical, and laboratory data of the patients are presented in Tables 1 and 2.

Incidence of liver steatosis and related factors

Hepatosteatosis was histologically present in 19 of 84 patients (22.6%). For patients with hepatosteatosis, 36.8% (7/19) showed mild, 36.8% (7/19) moderate, 21.1% (4/19) marked, and 5.3% (1/19) severe hepatosteatosis. The factors that were statistically correlated with hepatosteatosis were patient’s age, BMI, and triglyceride (TG) levels. In the hepatosteatosis group, the age (50.5 ± 8.7 years vs 35.2 ± 8.9 years, P < 0.01), BMI (32.9 ± 3.1 kg/m² vs 25.7 ± 3.3 kg/m², P < 0.01), and TG levels (188.3 ± 52.0 mg/dL vs 114.2 ± 44.2 mg/dL, P < 0.01) were higher compared to the group without hepatosteatosis. No significant correlation was found between hepatosteatosis and other parameters, such as HBeAg status, stage of fibrosis, HAI score, or HBV DNA level (≥ 30 copies/mL × 10⁶). In multivariate analysis, it was found that advanced age, increased BMI, and elevated TG levels were independent predictors of the presence of hepatosteatosis (Table 3).

Factors associated with SVR

Among 84 patients with CHB who received PEG-IFN therapy, 21.4% (18/84) showed SVR. The rate of SVR was 23.8% (5/21) in cases with HBeAg (+) and 20.6% (13/63) in cases with HBeAg (-). 88.6% (16/18) of CHB patients with SVR did not have any histopathologically determined steatosis. On the other hand, only two of the 19 CHB patients with liver steatosis - one with mild steatosis and the other one with moderate steatosis - had an SVR (10.5%). Although the SVR rate observed in patients without hepatosteatosis (16/65, 24.6%) was higher compared to those with hepatosteatosis (2/19, 10.5%), the difference was not statistically significant (P > 0.05). Using multivariate analysis, it was found that only ALT elevation was an independent predictor of SVR. No significant difference was found between SVR (+) and SVR (-) groups in terms of other parameters (Table 4).

Table 1  Demographic and clinical characteristics of the patients (mean ± SD)

| Parameter | n (%) |
|-----------|-------|
| Male | 60 (71.4) |
| Female | 24 (28.6) |
| Age (yr) | 38.6 ± 10.9 |
| HBeAg (+) | 21 (25.0) |
| HBeAg (-) | 63 (75.0) |
| Hypertension | 6 (7.1) |
| Diabetes mellitus | 3 (3.5) |
| BMI (kg/m²) | |
| < 25 | 27.4 ± 4.4 |
| 25-30 | 34 (40.5) |
| > 30 | 22 (26.2) |
| Glucose (mg/dL) | 101.4 ± 26.0 |
| Cholesterol (mg/dL) | 182.7 ± 29.3 |
| Triglyceride (mg/dL) | 131.0 ± 55.4 |
| AST (IU/L) | 103.3 ± 39.5 |
| ALT (IU/L) | 136.8 ± 47.2 |
| GGT (IU/L) | 49.9 ± 41.1 |
| ALP (IU/L) | 91.9 ± 26.5 |
| HBV-DNA (copies/mL × 10⁶) | 5502.9 ± 11889.7 |

HAI: Histological activity index.

Table 2  Histological characteristics of the patients

| Parameter | n (%) |
|-----------|-------|
| HAI score | |
| 0-3 | 5 (5.9) |
| 4-8 | 56 (66.7) |
| 9-12 | 22 (26.2) |
| 13-18 | 1 (1.2) |
| Stage of fibrosis | |
| 0 | 0 (0.0) |
| 1 | 7 (8.3) |
| 2 | 42 (50.0) |
| 3 | 35 (41.7) |
| 4 | 0 (0.0) |
| Steatosis | |
| None (0) | 65 (77.4) |
| Mild (<10%) | 7 (8.3) |
| Moderate (10%-30%) | 7 (8.3) |
| Marked (30%-60%) | 4 (4.8) |
| Severe (>60%) | 1 (1.2) |

HAI: Histological activity index.

Table 3  Comparison between patients with and without hepatosteatosis (mean ± SD)

| Parameter | Steatosis (+) (n = 19) | Steatosis (-) (n = 65) | P value |
|-----------|----------------------|----------------------|--------|
| Male | 14 (73.70) | 46 (70.80) | NS |
| Female | 5 (26.3) | 19 (29.2) | NS |
| Age (yr) | 50.5 ± 8.7 | 35.2 ± 8.9 | < 0.01 |
| BMI (kg/m²) | 32.9 ± 3.1 | 25.7 ± 3.3 | < 0.01 |
| HBeAg (+) | 18 (94.7) | 38 (58.5) | < 0.01 |
| Glucose (mg/dL) | 102.7 ± 27.7 | 96.7 ± 19.0 | NS |
| Cholesterol (mg/dL) | 192.2 ± 28.0 | 178.0 ± 27.4 | NS |
| Triglyceride (mg/dL) | 188.3 ± 52.0 | 114.2 ± 44.2 | < 0.01 |
| AST (IU/L) | 90.7 ± 34.8 | 107.0 ± 40.3 | NS |
| ALT (IU/L) | 128.3 ± 18.9 | 139.2 ± 25.2 | < 0.01 |
| GGT (IU/L) | 49.8 ± 29.8 | 50.0 ± 44.0 | NS |
| ALP (IU/L) | 91.8 ± 26.3 | 91.9 ± 26.7 | NS |
| HBV-DNA (copies/mL × 10⁶) | 5261.6 ± 2594.9 | 5684.2 ± 13245.8 | NS |
| HBeAg (+) | 4 (21.1) | 17 (26.2) | NS |
| HBeAg (-) | 15 (78.9) | 48 (73.8) | NS |
| Advanced fibrosis (score ≥ 3) | 8 (42.1) | 27 (41.5) | NS |
| Advanced HAI (score ≥ 9) | 6 (31.5) | 17 (26.2) | NS |
| SVR | 2 (10.5) | 16 (24.6) | NS |

BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-glutamyl transferase; ALP: Alkaline phosphatase; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; HAI: Histological activity index; SVR: Sustained viral response. NS: Non significant.
**Table 4** Comparison between patients with and without sustained viral response (mean ± SD)

| Parameter          | SVR (+) (n = 18) | SVR (-) (n = 66) | P value |
|--------------------|------------------|------------------|---------|
| Male               | 15 (72.2)        | 47 (71.2)        | NS      |
| Female             | 5 (27.8)         | 19 (28.8)        | NS      |
| Age (yr)           | 35.3 ± 8.0       | 39.7 ± 10.8      | NS      |
| BMI (kg/m²)        | 26.5 ± 3.1       | 27.9 ± 4.5       | NS      |
| Triglyceride (mg/dL)| 162.1 ± 23.7     | 175.6 ± 30.2     | NS      |
| Glucose (mg/dL)    | 97.4 ± 28.0      | 102.4 ± 25.5     | NS      |
| Cholesterol (mg/dL)| 109.7 ± 50.8     | 136.8 ± 28.5     | NS      |
| AST (IU/L)         | 172.2 ± 55.4     | 97.8 ± 28.5      | NS      |
| ALT (IU/L)         | 199.8 ± 82.0     | 122.3 ± 49.8     | <0.01   |
| GGT (IU/L)         | 62.9 ± 69.9      | 46.4 ± 28.6      | NS      |
| ALP (IU/L)         | 93.4 ± 38.8      | 91.5 ± 22.4      | NS      |
| HBV-DNA copies/mL| 4961.6 ± 2245.1  | 5779.5 ± 13129.5 | NS      |
| HBeAg (+) (copies/mL  × 10⁹) | 5 (27.8) | 16 (24.2) | NS      |
| HBeAg (-) (n = 16) | 5 (27.8) | 16 (24.2) | NS      |
| Advanced fibrosis  | 7 (38.9)         | 28 (42.4)        | NS      |
| (score ≥ 3)        | 5 (27.8)         | 18 (27.8)        | NS      |
| Advanced HAI       | 2 (11.1)         | 17 (25.8)        | NS      |
| Hepatosteatosis    | 2 (11.1)         | 17 (25.8)        | NS      |

BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ glutamyl transferase; ALP: Alkaline phosphatase; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen; HAI: Histological activity index; SVR: Sustained viral response. NS: Non significant.

**Table 5** Comparison between hepatitis B e antigen (+) patients with and without sustained viral response n (%)

| Parameter          | SVR (+) (n = 5) | SVR (-) (n = 16) | P value |
|--------------------|------------------|------------------|---------|
| Hepatosteatosis (+)| 1 (20)           | 3 (23)           | NS      |
| Hepatosteatosis (%)| 4 (80)           | 13 (77)          | NS      |

SVR: Sustained viral response. NS: Non significant.

**Table 6** Comparison between hepatitis B e antigen (-) patients with and without sustained viral response n (%)

| Parameter          | SVR (+) (n = 13) | SVR (-) (n = 50) | P value |
|--------------------|------------------|------------------|---------|
| Hepatosteatosis (+)| 1 (7.7)          | 14 (7.0)         | NS      |
| Hepatosteatosis (%)| 12 (92.3)        | 36 (93.0)        | NS      |

SVR: Sustained viral response. NS: Non significant.

was no difference in patients with or without steatosis regarding treatment response between the types of PEG-interferon (data not shown).

**Subgroup analysis according to the HBeAg status**

In HBeAg (-) patients, SVR was seen 7.7% (1/13) patients with hepatosteatosis, while it was 92.3% (12/13) without hepatosteatosis. Although the SVR rate was higher in the patients without hepatosteatosis, the difference was not statistically significant (Table 5).

In HBeAg (+) patients, SVR was seen in 20% (1/5) patients with hepatosteatosis while it was 80% (4/5) patients without hepatosteatosis. This difference was also not statistically significant (Table 6).

HBeAg seroconversion was seen in only four (19%) patients; all four patients had undetectable HBV DNA levels. None of our patients had HBSa seroconversion.

**DISCUSSION**

This study investigated the incidence and clinical importance of liver steatosis in patients with CHB. The factors associated with liver steatosis were determined. In patients who were given 48 wk PEG-IFN α therapy, the effects of liver steatosis and other factors upon persistent viral response were also investigated. In previous studies, the incidence of hepatosteatosis in patients with CHB was reported to range between 4.5% and 76%.[9-14] Especially in the studies where the alcohol consumers were not excluded, patients with CHB showed higher rates of hepatosteatosis[13,14]. In the present study, hepatosteatosis was histopathologically determined in 22.6% of CHB patients, and this prevalence is similar to that of the general population. Cases with other accompanying liver diseases, such as hepatitis C or alcohol consumers, were excluded and, thereby, misleading results were avoided.

In the development of non-alcoholic hepatosteatosis, insulin resistance constitutes the main mechanism.[15] Insulin resistance leads to hyperinsulinemia and an increase in free fatty acid concentrations, resulting in TG accumulation in hepatocytes.[16] Insulin might also play an important role in the development of fibrosis accompanied by hepatosteatosis by activating the profibrogenic pathways.[18] The cause and clinical importance of hepatosteatosis accompanying CHB are not well defined. In previous studies, non-alcoholic hepatosteatosis seen in patients with CHB was related to advanced age, large waist circumference, high fasting GLU and C-peptide levels, HTA, or dyslipidemia.[10,26] In the present study, we found that advanced age, higher BMI, and elevated TG levels were independent risk factors of hepatosteatosis in patients with CHB. Hepatosteatosis and fibrosis scores, however, were not correlated.

The virus by itself might be the cause of the hepatosteatosis as seen in some CHC patients with hepatic steatosis.[21] However, we did not find any correlation between hepatosteatosis and viral factors, such as HBeAg status, HBV DNA level, and HAI. Taken together, the presence of steatosis correlates with some host factors (advanced age, high BMI, and TG levels), but not with viral genotype or viral load. Accordingly, the results of the present study support the finding that metabolic factors, rather than viral factors, are more determinant for hepatosteatosis encountered in cases with CHB[23] and that, whereas the association between steatosis and HCV is specific, this is not the case in HBV-infected patients.

Hepatosteatosis is related to metabolic factors, and hepatitis C virus infection per se leads to hepatosteatosis.
directly in different genotypes (in genotype 2 and 3)[23]. The presence of liver steatosis in chronic viral hepatitis B might vary according to different genotypes, as reported in CHC[24,25]. In the present study, HBV genotyping could not be performed due to lack of laboratory resources. Nevertheless, hepatitis B infection in Turkey is accepted to be virtually all genotype D (almost 100%); hence, a genotype effect is not expected, and analyzing the genotype is not recommended as cost-effective in such studies.

Treatment of CHB is a big challenge. The response rates are still low despite novel therapy strategies. Besides the viral factors, other accompanying conditions might hamper the success of a therapy: Hepatosteatosis encountered in other chronic liver diseases not only has the potential to influence the progression of diseases, but is also suggested to diminish the response to the given therapy.[28]

In the literature, there is only one study that retrospectively investigated the effect of co-existent steatosis upon the response to treatment in CHB patients.[29]. That study reported that the presence of steatosis does not have any effect on the outcome of the treatment. In the present study, persistent viral response to 48 wk of PEG-IFN was 21.4%, which was consistent with previous studies.[25,26]. As a support for the study of Moucari et al[26], only ALT elevation was an independent predictor of SVR. Strikingly, 88.9% (16/18) of CHB patients with SVR did not have any histopathologically determined steatosis. On the other hand, only two of the 19 (10.5%) CHB patients with liver steatosis had SVR. The high SVR rates obtained in patients without hepatosteatosis compared to those with hepatosteatosis, however, were not significant statistically. The fact that hepatosteatosis has no statistically significant effect on SVR may be due to our small number of patients.

It would be better if the homeostasis model assessment (HOMA) could also be determined. However, HOMA was designed to determine the relationship between chronic viral hepatitis and the presence of steatosis with respect to the effect upon treatment of viral hepatitis. The role of risk factors of steatosis, including the GLU HOMA index upon the course of chronic viral hepatitis B patients with steatosis, was beyond the scope of this study. This will be the subject of future studies.

In conclusion, hepatosteatosis is encountered frequently in patients with CHB. This association leads to a trend of decreased, but statistically insignificant, sustained viral response rate to PEGylated interferon treatment both in hepatitis B e antigen (HBeAg) (+) and HBeAg (-) patients.

 Applications
Hepatic steatosis, a risk-free, benign condition in healthy subjects, might become a dangerous co-factor of disease progression when it is present in patients affected by another liver disease. It might affect the response to antiviral treatment and the significant negative effect of hepatosteatosis upon response to therapy in CHB patients should be demonstrated using larger prospective studies. Given the importance of advanced age, BMI, and high levels of TG as being independent risk factors for development of hepatic steatosis, treatment strategies against obesity and TG elevations would have positive effects on CHB progression and the response to the given therapy. Hence, combating steatosis and its associated factors might aid in increasing the response to therapy in CHB patients.

COMMENTS
Background
Fatty livers encountered frequently in clinical practice may co-exist with other chronic liver diseases, and can influence the progression of the chronic liver diseases with different etiologies. The number of studies reporting co-existence of steatosis and chronic hepatitis B (CHB) is increasing. The impact of superimposed non-alcoholic fatty liver disease in patients with CHB, however, is less clear.

Research frontiers
Fatty livers are more vulnerable to factors associated with further hepatic injury because of their increased sensitivity to oxidative stress and cytokine-mediated hepatic damage, which may lead to chronic liver disease. The presence of a fatty liver can influence the progression of the chronic liver diseases with different etiologies and the response to given therapy. Steatosis of the liver in patients with chronic hepatitis C increases the severity of fibrosis and unfavorably influences the response given to therapy. Nevertheless, the association of liver steatosis and CHB, a major cause of chronic liver disease worldwide, is less clear.

Innovations and breakthroughs
Hepatosteatosis is not infrequent in patients with CHB. Advanced age, body mass index (BMI), and high levels of triglyceride (TG) are independent risk factors for the development of hepatic steatosis in patients with chronic viral hepatitis B. This coexistence leads to a trend of decreased, but statistically insignificant, sustained viral response rate to PEGylated interferon treatment both in hepatitis B e antigen (HBeAg) (+) and HBeAg (-) patients.

Applications
Hepatic steatosis, a risk-free, benign condition in healthy subjects, might become a dangerous co-factor of disease progression when it is present in patients affected by another liver disease. It might affect the response to antiviral treatment and the significant negative effect of hepatosteatosis upon response to therapy in CHB patients should be demonstrated using larger prospective studies. Given the importance of advanced age, BMI, and high levels of TG as being independent risk factors for development of hepatic steatosis, treatment strategies against obesity and TG elevations would have positive effects on CHB progression and the response to the given therapy. Hence, combating steatosis and its associated factors might aid in increasing the response to therapy in CHB patients.

Peer review
This study, even is observational, is fairly interesting.

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