Prevalence of Hepatic Steatosis in Chronic Hepatitis B Patients and Its Association with Disease Severity

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ABSTRACT

Aim: to know the prevalence of liver steatosis in chronic hepatitis B (CHB) patients and evaluate whether its presence was associated with a more progressive disease. Methods: a cross-sectional study was conducted in Cipto Mangunkusumo and Medistra Hospitals, Jakarta on CHB patients between 2007 and 2009. Data on patients’ demography, anthropometry, liver function test and hepatitis B serology were collected. Hepatic steatosis was assessed by liver biopsy and graded as mild (<33%), moderate (33-66%) or severe (>66%). Fibrosis stage and necroinflammatory activity were assessed according to the METAVIR system. Results: one-hundred and seventy-four patients were enrolled; 99 (56.9%) among them were men. Patients’ mean age was 39.9±10.69 years. About 56% of cases were HBeAg negative. The prevalence of liver steatosis was 29.9%. Patients with liver steatosis had significantly higher body mass index (25.1±3.3 vs. 22.7±3.3 kg/m², p<0.001) and waist circumference (88.3 vs. 79.0 cm; p<0.001) that were higher than those without steatosis. There were no differences of log HBV-DNA levels (5.72±1.993 vs. 6.07±2.077; p=0.675) and liver stiffness (8.3±6.28 vs. 9.5±10.18 kPa) between patients with and without steatosis. Fibrosis (61.5% vs. 69.7%; p=0.295) and necroinflammation (63.5% vs. 65.6%; p=0.789) did not differ significantly between patients with and without steatosis. No association between liver steatosis and HBeAg status (p=0.736). Conclusions: steatosis hepatis was found in 30% of CHB patients. Its presence was most often associated with obesity. Unlike hepatitis C patients, hepatic steatosis in CHB patients is not associated with more progressive disease.

Kata kunci: steatosis hepatis, hepatitis B kronik, fibrosis hati.
INTRODUCTION

Hepatic steatosis is the accumulation of lipid droplets in hepatocytes characterized by microvesicular and/or macrovesicular steatosis.\(^1\) Hepatic steatosis is a common finding in patients with chronic hepatitis B (CHB) with prevalence varies from less than 20\(^\%\)\(^{2,3}\), 30-40\(^\%\)\(^{4,5}\) to more than 55\%.\(^{6,7}\) There is no explanation why the prevalence varies greatly among studies. Altogether, the presence of hepatic steatosis in CHB was considered low compared to those occurring in chronic hepatitis C (CHC); in which viral factors contributes directly to the development of insulin resistance and fat accumulation in the liver.\(^8\)

The impact of hepatic steatosis on the natural course of CHB is less recognized compared to those known in chronic hepatitis C patients. While CHB patients have increased risk of developing cirrhosis and hepatocellular carcinoma (HCC), recently non-alcoholic fatty liver (NAFLD) has also been regarded as a risk factor for HCC.\(^9\) Therefore, it is tempting to know whether the presence of hepatic steatosis is associated to a more progressive disease, such as liver fibrosis and cirrhosis.

The prevalence of hepatic steatosis in CHB patients and its impact has not been studied in Indonesia. Therefore, this study was primarily aimed to find the prevalence of hepatic steatosis in CHB patients and secondarily to evaluate whether its presence was associated with disease severity in terms of serum alanine aminotransferase (ALT) and hepatitis B virus deoxyribonucleic acid (HBV-DNA) levels, hepatitis B e antigen (HBeAg) status, liver fibrosis and necroinflammatory grade.

METHODS

Study Design and Subjects

A cross-sectional study was done in Cipto Mangunkusumo Hospital and Medistra Hospital, Jakarta on CHB patients between 2007 and 2010. Patients were included if they were willing to undergo liver biopsy. Data on patients’ demography, anthropometry, liver function test and hepatitis B serology were collected. Body mass index (BMI) was calculated as body weight in kilograms divided by body height in meter square (kg/m\(^2\)). Obesity was defined by a body mass index of more than 25 kg/m\(^2\) for Asian population, according to the World Health Organization.

Laboratory Procedures

Blood chemistry test was done by using automated blood analyzer (Advia Hematology Analyzer, Siemens Diagnostics, Bad Nauheim, Germany). Hepatitis B serology markers, i.e. HBsAg, HBeAg, and anti-HBe were checked using the enzyme-linked immunosorbent assay (ELISA) with commercial kits. Quantitative serum HBV-DNA level was measured using the polymerase chain reaction technique (COBAS® TaqMan HBV Test, Roche Diagnostics, Basel, Switzerland). The lower detection limit was 4,700 copies/mL. Genotype analysis was performed using specific primers.

Liver Biopsy

Liver biopsy was performed using a 16-gauge Menghini needle (Hepafix, Braun, Melsungen AG, Germany) under local anesthesia. The specimens then were fixed in formalin and embedded in paraffin blocks. A 4-μm thick of the specimens were cut and stained with hematoxylin eosin. Fibrosis was assessed with Masson trichrome staining. Histopathology assessment was done by an experienced pathologist, who was blinded to the patients’ clinical history. Adequate specimens should be at least 15 mm long and includes 5 portal systems. The degree of steatosis was graded 1 to 3, according to the percentage of cells with fatty droplets (grade 1: (mild) 0-33\%, grade 2 (moderate): 34-66\%, grade 3 (severe): 67-100\%). The stage of fibrosis
was measured based on the META VIR scoring system (F0 = normal connective tissue; F1 = foci of perivenular and/or perisinusoidal fibrosis in zone 3; F2 = perivenular or pericellular fibrosis affecting zones 3 and 2; F3 = septal or bridging fibrosis; and F4 = cirrhosis).\textsuperscript{11,12}

**Liver Stiffness Measurement**

The liver stiffness was measured using Fibroscan (Echosens, Paris, France). Examination procedure was done according to the previous technical description.\textsuperscript{13} Ten successful measurements were performed on each patient. The success rate was calculated as the number of validated measurements divided by the total number of measurements. The results were expressed in kilopascals (kPa). The median value of successful measurements was considered representative of the liver stiffness in a given patient, according to the manufacturer’s recommendation (interquartile range [IQR] less than 30% of the median value and success rate >60%).\textsuperscript{14}

**Statistical Analyses**

Characteristics of the study subjects were presented descriptively; continuous variables were expressed as mean ± standard deviation or median (range) while categorical variables were presented as frequency and percentage. The association between liver steatosis and disease severity (serum alanine aminotransferase, serum HBV-DNA levels, fibrosis stage and necroinflammatory grade according to META VIR Score) was analyzed statistically. Mean comparison was tested using the Mann-Whitney U test. A p value of <0.05 was considered significant. Statistical analysis was performed using the software Statistical Program for Social Studies version 13.0 for Windows PC (SPSS Inc, Chicago, IL, USA).

**RESULTS**

There were 174 cases eligible for analyses; 99 (56.9%) among them were men. Patients’ mean age was 40.8±11.00 years, spanning from 16 to 70 years. About 56% of all cases were HBeAg negative. Viral genotype data were available in 125 cases; 96 (76.8%) were genotype B (Table 1).

Hepatic steatosis was present in 52 (29.9%) patients; 38 (73.1%) of them were mild steatosis. The presence of hepatic steatosis was significantly associated with higher body mass index and waist circumference. Serum ALT and HBV-DNA levels did not significantly differ in both groups. No association among hepatic steatosis, HBeAg status, hepatitis B viral genotype, and the presence of significant fibrosis or necroinflammatory grade. Liver stiffness measurement showed similar values between patients with and without hepatic steatosis (Table 2).

**DISCUSSION**

This is the first study in Indonesia assessing hepatic steatosis among CHB patients. Almost 30% of our cases had some fat accumulation in the liver. This number was close to the reported prevalence by two studies in Turkey\textsuperscript{4,5} but much differed from other studies.\textsuperscript{2,3,6,7} So far there is no explanation why hepatic steatosis prevalence varies greatly among studies. However, our number might reflect the true prevalence of NAFLD in Indonesian population which was also found around 30%.\textsuperscript{15}
Initial data suggest that hepatic steatosis in CHB is related to host factors such as metabolic syndrome or its component. In accordance to previous reports, we found that hepatic steatosis was significantly associated with higher body mass index and waist circumference. Many studies have reported the association of hepatic steatosis and metabolic factors such as obesity or high body-mass index, waist circumference, hypertriglyceridemia, hyperglycemia, diabetes, and insulin resistance. Therefore, experts believe that host factors were responsible to intra-hepatic fat accumulation in CHB patients.

On the other hand, there is also no evidence that viral factors cause insulin resistance which was seen in patients with CHC. It appears that hepatic steatosis did not affect the natural course of CHB and may only reflect the host metabolic profile. In the current study, we found that hepatic steatosis tended to present more among patients with viral genotype C (37.9%) compared to genotype B (24.0%). HBV genotype C has been regarded as a less favourable type compared to viral genotype B since it is associated to more chronicity and less response to antiviral treatment. However, whether this viral type contributes to hepatic steatogenesis is largely unknown. No other study has associated viral genotype with hepatic steatosis and the concept of steatogenic genotypes for HBV remains speculative. There are experimental data showing that increased HBV X protein could induce lipid accumulation in the hepatocytes, but clinical data do not support this finding.

All studies conducted so far, including ours, had been done on archival data. Thus, the impact of hepatic steatosis on the natural history of CHB in long-term follow-up cohort was unknown. However, the fact that steatosis was not associated with fibrosis stage suggested that it was only a co-existence disease without negative consequence. Liver stiffness measurement supported this finding (Table 2). Even when cases were selected to include only patients with fibrosis stage 2 or less (data not shown), the mean liver stiffness did not differ between patients with and without hepatic steatosis (6.43 vs. 6.75; p=0.749). It should be noted, however; that our subjects were predominated by mild degree of steatosis which might not have clinical consequence at all.

Another version of this kind of study has been conducted in India, where insulin resistance (IR) among CHB patients was studied in more details. The investigators found that IR was present in 49.3% of CHB patients, but there was no significant association between IR and worsening liver fibrosis. Thus, although IR was quite prevalent in CHB, its presence was only a reflection of the host metabolic profile and did not affect histological severity.

**CONCLUSION**

Liver steatosis was found in 30% of chronic hepatitis B patients. Its presence was mostly associated with central obesity. Unlike chronic hepatitis C, liver steatosis in chronic hepatitis B was not related to a more progressive disease.

**REFERENCES**


