Effects of Metabolic Syndrome on Fibrosis in Chronic Viral Hepatitis

Harry Yoon*, Jeong Gui Lee*, Jeong Hwan Yoo*, Myung Su Son*, Dae Young Kim*, Seong Gyu Hwang*,† and Kyu Sung Rim*†

*Department of Internal Medicine and †Institute of Gastroenterology, CHA University, Seongnam, Korea

Background/Aims: Metabolic syndrome, comprising diabetes, hypertension, central obesity, and dyslipidemia, is increasingly prevalent worldwide. We aimed to study the relationship between metabolic syndrome and the risk of liver fibrosis in patients with chronic hepatitis B (CHB) and chronic hepatitis C (CHC).

Methods: In total, 954 patients (CHB, 850; CHC, 104 patients) with liver biopsy were included in the retrospective analysis. Extensive clinical and histological data were available. Metabolic syndrome was defined using the International Diabetes Federation definition of metabolic syndrome, 2006 criteria. Histological lesions were evaluated according to the histology activity index system.

Results: Metabolic syndrome was present in 6% of patients and significantly more prevalent in patients with CHC than in patients with CHB (5% vs 13%, p<0.001). Patients with metabolic syndrome were older among patients with CHB and patients with CHC, and, as expected, were mainly overweight or obese. Fibrosis was significantly more severe in patients with metabolic syndrome than in those without, regardless of whether they had CHB and CHC (CHB, 3.3±2.1 vs 2.4±1.3, p=0.025; CHC, 2.6±1.5 vs 1.3±0.7, p=0.006). Liver fibrosis (stages 3 to 4) was independently associated with increased age, higher transaminase level and metabolic syndrome (odds ratio, 2.421; p=0.017).

Conclusions: Metabolic syndrome is associated independently with severe fibrosis in patients with chronic viral hepatitis B and C.

Key Words: Metabolic syndrome; Hepatitis B; Hepatitis C; Liver cirrhosis

INTRODUCTION

Metabolic syndrome, which has close association with insulin resistance, consists of central obesity, type 2 diabetes mellitus (DM), hypertension and hyperlipidemia, and the prevalence is increasing.1 There have been also reports that adipokines, such as leptin and adiponectin, secreted in patients of metabolic syndrome may cause liver fibrosis in chronic liver disease patients.2-4 Various studies have already reported the association between liver fibrosis and metabolic syndrome in nonalcoholic fatty liver disease (NAFLD)5-6 and found that the components of metabolic syndrome are independent risk factors of liver fibrosis.7-9 There are relatively less data on chronic viral hepatitis, however. With regards to chronic hepatitis C (CHC), studies have reported that type 2 DM and other components of metabolic syndrome negatively affects the efficiency of antiviral treatments.10-12 According to previous report,13 the prevalence of diabetes and metabolic syndrome were raised in CHC patients, with accelerated progression of liver fibrosis. There are even less information regarding chronic hepatitis B (CHB) than CHC. Only a few preliminary data suggested association between the components of metabolic syndrome—obesity, diabetes, hypertension, and hyperlipidemia—and liver fibrosis in CHB.14,15

The aim of this study was to determine the association between metabolic syndrome and liver fibrosis in CHB and CHC.

MATERIALS AND METHODS

1. Study population

CHB or CHC patients who received liver biopsy in the gastroenterology department of CHA Bundang Medical Center, CHA University between May 2000 and May 2010 participated in the study. Liver biopsy was done mainly to make a firm diagnosis and to help provide information about the severity of chronic viral hepatitis. Biopsies were often indicated in such patients to exclude other causes of liver disease and to help provide information about the severity of the viral hepatitis. The major other causes of liver disease, which may be present instead of...
or in addition to chronic viral hepatitis, include alcoholic liver disease, drug- or toxin-induced liver disease, fatty liver disease, autoimmune liver disease, other inflammatory or infectious liver disease including granulomatous hepatitis, and a variety of metabolic diseases. Those with an evidence of other chronic liver disease were excluded from the study. Patients less than 18 years old; patients with neoplasm including hemangiomma, liver cyst, and hepatocellular carcinoma; coinfection of hepatitis B and C; hepatitis B healthy carrier with normal transaminase; alcoholic liver disease (20 g/day or more for males, 10 g/day or more for females); autoimmune hepatitis; and metabolic liver diseases such as Wilson’s disease were other criteria of exclusion.

2. Methods

1) Biological and clinical parameters

A retrospective, cross-sectional study was performed by collecting clinical parameters, laboratory data and biopsy reports from the search of medical records and electronic records. Medical records were referred for patients’ past medical histories such as drug and alcohol use and family history. Diabetes, hypertension or hyperlipidemia was defined as a medical history when they were clinically diagnosed and in need of medical therapy. Heights and weights measured from each patient at visit were used to calculate the body mass index (BMI; kg/m²). Morning fasting blood samples was collected to measure biochemical values of fasting glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglyceride (TG), total cholesterol, low density lipoprotein, high density lipoprotein (HDL), albumin, complete blood count, viral marker, γ-glutamyl transferase, and creatinine.

Metabolic syndrome was defined as having BMI of 30 kg/m² or more and any two of the following four components, according to the International Diabetes Federation consensus worldwide definition of the metabolic syndrome, 2006.

(1) Fasting glucose >100 mg/dL.
(2) TG >150 mg/dL.
(3) HDL-cholesterol <40 mg/dL in males, <50 mg/dL in females
(4) Blood pressure >130/85 mm Hg

2) Liver histology

Histologic findings were categorized based on the severity of fibrosis, according to histology activity index (HAI) system. With their 1981 publication, Knodell et al.16 introduced semi-quantitative and reproducible histological scoring of liver biopsies. Lesions were assigned weighted numeric values, which resulted in a score, the HAI (Table 1).17 The HAI comprised three categories for necroinflammation and one for fibrosis, with points for the severity of the lesion in each category. The sum total of points constituted the final score, or HAI. In this study, we used only fibrosis score. Fibrosis scoring was assessed by one expert pathologist blinded to clinical information of patients.

3) Statistical analysis

PASW version 18.0 software (IBM Co., Armonk, NY, USA) was used for statistical analysis. A t-test was used for comparison between groups, and logistic regression test was used for multivariate analysis. The results were presented as mean±standard deviation. A p-value of less than 0.05 was defined as statistically significant.

RESULTS

1. Clinical characteristics of study population

Among a total of 954 patients who were included in the analysis, 850 patients had CHB and 104 patients had CHC. The 63.3% of CHB patients and 57.5% of CHC patients were male. The mean age was 43.2 and 48.7, respectively. Statistically significant differences were not found between the two groups. Clinical features of the overall patients are presented in Table 2.

Table 1. Grading and Staging of the Histopathological Lesion of Liver Biopsy: Histology Activity Index (HAI-Knodell Score)

| Periportal bridging necrosis | Score | Intralobular degeneration and focal necrosis | Score | Portal inflammation | Score | Fibrosis | Score |
|-----------------------------|-------|---------------------------------------------|-------|---------------------|-------|----------|-------|
| None                        | 0     | None                                        | 0     | No portal inflammation | 0     | No fibrosis | 0     |
| Mild piecemeal necrosis     | 1     | Mild                                        | 1     | Mild                | 1     | Fibrous portal expansion with septae formation | 1     |
| Moderate piecemeal necrosis| 3     | Moderate                                    | 3     | Moderate            | 3     | Bridging fibrosis (portal-portal or portal-central linkage) | 3     |
| Marked piecemeal necrosis   | 4     | Marked                                      | 4     | Marked              | 4     | Cirrhosis | 4     |
| Moderate piecemeal necrosis plus bridging necrosis | 5 | - | - | - | - | - | - |
| Marked piecemeal necrosis plus bridging necrosis | 6 | - | - | - | - | - | - |
| Multilobular necrosis       | 10    | -                                           | -     | -                   | -     | -        | -     |
2. Prevalence of metabolic syndrome and its components

The overall prevalence of metabolic syndrome was 6% (56/954); the prevalence was lower in CHB than in CHC (5% vs 13%, p<0.001). Among the components of metabolic syndrome, fasting glucose >100 mg/dL was more frequent in CHB (24% vs 18%, p=0.041), while TG >150 mg/dL was more frequent in CHC (9% vs 20%, p=0.006) (Table 3).

3. Comparison in terms of the presence of metabolic syndrome

Clinical features according to the presence of metabolic syndrome in CHB and CHC are presented in Table 4. Both CHB and CHC were associated with older age and greater BMI in the presence of metabolic syndrome. Both groups showed increased frequency of diabetes, hyperlipidemia, hypertension, and fasting glucose in the presence of metabolic syndrome; however, alcohol consumption, history of antiviral therapy, AST/ALT, and total bilirubin were not significantly different between the two groups. The extent of liver fibrosis was found more serious when accompanying metabolic syndrome in both groups (CHB, 3.3±2.1 vs 2.4±1.3, p=0.025; CHC, 2.6±1.5 vs 1.3±0.7, p=0.006).

4. Predictors of liver fibrosis

Predictors of liver fibrosis were analyzed in the patients with CHB and the patients with CHC. Patients in both groups were stratified to stages 0 to 2 or 3 to 4, according to the extent of fibrosis on the histologic findings, to compare differences between the groups using univariate analysis (Table 5). Old age, BMI, increased AST/ALT, and metabolic syndrome showed as association with advanced fibrosis (fibrosis stages 3 to 4) in both CHB group and CHC group. And in CHB, alcohol consumption was associated with advanced fibrosis (fibrosis 0 to 1, 42.4%; 3 to 4, 71.31%; p=0.042).

A multivariate analysis using the variables which showed association in the univariate analysis was performed to determine if the presence of metabolic syndrome, or its components, could be independent factors of the advanced liver fibrosis (Table 6). Metabolic syndrome was found as an independent predictor of liver fibrosis in both CHB and CHC (CHB odds ratio, 2.421, p=0.017; CHC odds ratio, 2.751, p=0.027), with at least two times risk of developing liver fibrosis.

Another analysis was performed to determine if the risk of liver fibrosis could be changed based on how many of the five components of metabolic syndrome were met (Table 7) but no significant association was found either in CHB or CHC.

DISCUSSION

The purpose of this study was to find association between metabolic syndrome and liver fibrosis in CHB and CHC, which are the most common causes of chronic liver disease. The association between chronic viral hepatitis and metabolic syndrome was reported in several previous studies. One previous study reported that CHC increases the risk of type 2 DM through its direct influence on glucose and lipid metabolism. Other report
concluded that the prevalence of diabetes and metabolic syndrome were raised in CHC with increased risks of NAFLD and liver fibrosis. Despite lack of data on the association with CHB compared to CHC, there was a report that women with CHB were more likely to have gestational diabetes, but there is still no report that metabolic syndrome may interfere with the treat-
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In this study, the prevalence of metabolic syndrome was 6% in overall, 5% in CHB, and more increased 13% in CHC. This lower prevalence of metabolic syndrome in CHB compared to CHC might be explained by lower BMI and age in the CHB group (age, 43.2±15.2 vs 48.7±9.8; BMI, 24.2±7.6 vs 25.2±4.8) although these data were not statistically significant and higher prevalence of TG >150 mg/dL in CHC (9% vs 20%, p=0.006). Various epidemiologic studies have actually reported higher prevalence of metabolic syndrome in groups with greater BMI and older age.20-22 The overall prevalence of 6% in this study was lower than that of general population. It is speculated that hypocholesterolemia due to hypobetalipoproteinemia in CHC patients33 might have had influence on this result, which is why this study in chronic viral hepatitis patients had lower prevalence than studies in general population.

The most significant conclusion of this study is the presence of independent association between metabolic syndrome and liver fibrosis in both CHB and CHC, which was also reported in other previous studies. Previous study33 reported that the feature of NAFLD in CHC had an association with metabolic syndrome, suggesting that it could be a predictor of advanced fibrosis; however, they did not mention any correlation with histologic severity or the difference in terms of the five components of metabolic syndrome. In our study, not all five components of metabolic syndrome showed independent correlation with liver fibrosis nor was there a linear causality based on the number of components a patient had, but the presence of metabolic syndrome showed the most independent correlation with liver fibrosis.

The most important limitation of this study is the comparatively small number of subsets satisfying the criteria of metabolic syndrome, which could contribute to the possibility of overestimation due to type 2 error. Being a retrospective, cross-sectional study, we used the anthropometric and biochemical data measured at liver biopsy for evaluation, which could have made establishing causal relationship more difficult. A follow-up study in a bigger sample is required to determine the change of association with the predictor over time.

In conclusion, metabolic syndrome showed independent association with liver fibrosis both in CHB and CHC. Clinicians might need to monitor chronic viral hepatitis patients with the possibility of metabolic syndrome in mind. Therapeutic interventions for metabolic syndrome, upon its diagnosis, could improve the prognosis of the patient. Weight reduction, glucose control and adequate control of the blood pressure and hyperlipidemia are recommended for chronic viral hepatitis patients with signs of metabolic syndrome.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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