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Full Length Research Paper

Metabolic syndrome and severity of fibrosis in patients with chronic viral hepatitis B infection or non-alcoholic fatty liver disease

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To investigate the prevalence of metabolic syndrome (MS) in patients with chronic viral hepatitis B (HBV) infection or non-alcoholic fatty liver disease (NAFLD), and to determine the relationship between MS and the risk of fibrosis in those patients, 136 patients with chronic HBV infections and 110 NAFLD patients were analyzed retrospectively between January 2008 and June 2009. The results showed that the prevalence of MS in the NAFLD group was significantly higher that of the HBV infection group (49.1 and 11.8%, respectively; P < 0.01). In HBV group, severity of fibrosis was associated with increased body mass index (BMI), higher aspartate aminotransferase (AST) and gamma-glutamyl-transpeptidase (GGT), severity of necroinflammation and MS. However, in NAFLD group, MS was more prevalent in patients with non-alcoholic steatohepatitis (NASH) than that of simple fatty liver (55.4 and 40%, respectively; P < 0.01). Severity of fibrosis was associated with MS, higher alanine transarninase (ALT), AST, GGT, and severe necroinflammation. We concluded that MS might be more prevalent in NAFLD patients, and associated with the severity of fibrosis in patients with chronic HBV infection or NAFLD.

Key words: Metabolic syndrome, viral hepatitis B, non-alcoholic fatty liver disease, fibrosis.

INTRODUCTION

Metabolic syndrome is caused by the interactions among multiple metabolic risk factors of cardiovascular disease. Chinese diabetes society suggests that the individuals could be diagnosed as metabolic syndrome by the presence of at least three of four specific symptoms, including overweight or obesity, hyperglycemia, hypertension and dyslipidemia. Nonalcoholic fatty liver disease (NAFLD) is closely related with metabolic syndrome, and the NAFLD patients have the risk to develop the hepatocirrhosis and hepatic carcinoma eventually (Farrell and Larter, 2006; Nugent and Younossi, 2007). Patients with chronic hepatitis C have a relatively higher prevalence of NAFLD and metabolic syndrome, which could promote the liver fibrosis and reduce the body response rates to interferon therapy (Poynard et al., 2003; Tsochatzis et al., 2007). However, the association betwe en metabolic syndrome and chronic hepatitis B infection remains unclear now. The aim of this study was to understand the prevalence of metabolic syndrome in patients with chronic HBV infection, as well as the correlation between metabolic

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syndrome and liver injure by comparing with NAFLD.

MATERIALS AND METHODS

Samples

136 patients with chronic HBV infection and 110 patients, who all underwent liver biopsy with NAFLD for primary hospitalization, were recruited in our hospital between January 2008 and June 2009. Of 136 chronic HBV patients there were 103 males and 33 females with a median age of 34.52 ± 9.97 years, range from 23 to 56 years, with a case history between 0.8 to 25 years, 26 individuals had been received or was undergoing the antiviral therapies. Of 110 NAFLD patients, 86 cases were male and 24 cases were female whose ages were in the range of 37.43 ± 10.51 with a case history between 0.3 to 31 years. The diagnosis criterion for chronic hepatitis B was carried out according to guideline for prevention and treatment of chronic hepatitis B drawn up by Chinese Society of Hepatology and Society of Infectious Diseases in 2005, which indicates the history of HBV infection or the positive HBsAg of hepatitis B is longer than six months, and the HBsAg remains positive. The diagnosis criterion for NAFLD was performed by guidelines for diagnosis and treatment of nonalcoholic fatty liver diseases defined by fatty liver and alcoholic liver disease study group of Chinese Society of Hepatology in 2005. Chronic hepatitis B patients with longer than 6 months of HBsAg positive history, HBeAg positive or negative, HBV-DNA>10^3copies/ml and serum ALT values higher than or at the normal level, or the NAFLD patients with type-B ultrasonic, computed tomography and other imaging or historical examination test results met the diagnosis criterions for NAFLD were included in this study. Individuals infected with other types of virus (like hepatitis C virus, hepatitis D virus, human Immunodeficiency virus, etc.) or different types of liver diseases (drug induced, autoimmune, metabolic or alcoholic liver diseases, etc.), or treated with antiviral therapy were excluded.

Clinical evaluation

Basic characteristics were obtained from all the patients, including sex, age, height, body weight, body mass index (BMI), blood pressure and history of alcohol abuse, diabetes, hypertension, hyperlipidemia and coronary heart disease. Metabolic syndrome was diagnosed in the presence of at least three criteria out of five defined by the Adult Treatment Panel III recommended by Asia-Pacific in 2007(Fan et al., 2007), namely: (1) waist circumference ≥ 90 cm in men and ≥ 80 cm or the BMI ≥ 25 kg/m^2 in women; (2) triglyceride ≥ 1.7 mmol/L or under therapy; (3) HDL cholesterol < 1.03 mmol/L in man and < 1.29 mmol/L in women; (4) blood pressure ≥ 130/85 mm Hg(1 mm Hg=0.133 kPa) or be diagnosed as hypertension before or during the therapy; (5) fasting glucose ≥ 5.6 mmol/L or be diagnosed as diabetes before or during the therapy. Alcohol abuse was considered as a mean weekly alcohol consumption >140 g/week in men and >70 g/week in women.

Experimental methods

Blood chemistry tests were performed using 15 ml of fasting venous blood drawn 24 h before the liver biopsy for all the patients, including continuous monitoring assay of serum alanine aminotransferase, aspartate transaminase and γ-glutamyltransferase, oxidase method of fasting glucose, enzymatic analysis of serum triglyceride and total cholesterol, direct assay of serum HDL cholesterol, and coupling method of uric acid (7180 Automatic Analyzer, Hitachi High-Tech Science Systems Corporation, Japan) were performed. Viral examinations indicators, including HBsAg, HBeAg and HBV-DNA loads were evaluated as well.

Liver histology

All 246 liver tissues with length of 1.0 to 2.0 cm were collected by disposable 16G bard biopsy needle, fixed in 4% paraformaldehyde, dehydrated, paraffin embedded, serial sectioned, and evaluated by the same experienced pathologist. Fatty liver was graded into four degrees according to the hepatocyte count with steatosis inside hepatic lobules: F_0, less than 5% of hepatocytes with steatosis; F_1, 5 to 30% of hepatocytes with steatosis; F_2, 31 to 50% of hepatocytes with steatosis; F_3, 51 to 75% of hepatocytes with steatosis; F_4, more than 75% of hepatocytes with steatosis. Liver flammation grades (G) and fibrosis stages (S) of liver tissue infected with chronic HBV were decided to follow A project for the prevention and treatment of viral hepatitis established by Society of Infectious Diseases, CMA and Chinese Society of Hepatology, CMA in 2000.

Statistical analysis

All data were analyzed using statistical package for social science (SPSS version 13.0). Count information was represented by rate, and the quality data was expressed as $\bar{x}$ ±s. Mean differences between the groups were analyzed by t test, while χ^2 test was used for the comparisons of the rates. Statistical significance was taken as $P < 0.05$.

RESULTS

One hundred and fifty patients infected with chronic hepatitis B virus, and one hundred twenty NAFLD patients were recruited in this study between January 2008 and June 2009, of which, fourteen chronic HBV patients and ten NAFLD patients were excluded due to the incomplete data. Chronic HBV group and NAFLD group had no statistical significance in sex, serum alanine aminotransferase, aspartate transaminase, triglyceride level and severity of inflammation ($P > 0.05$ for all). Compared to chronic HBV group, NAFLD group had older ages, larger body mass index, significant increase of γ-glutamyltransferase, total cholesterol, fasting blood glucose and uric acid in serum, more severe fatty degeneration in liver, and lower in both HDL-C level and severity of liver fibrosis($P<0.05$ for all) (Table 1).

Prevalence of metabolic syndrome in chronic HB and NAFLD patients was 28.5% (70/246), which was 49.1% (54/110) in chronic HBV group and significant higher than that (11.8%, 6/136) in NAFLD group (χ^2=41.618, $P<0.01$). There was no statistic significance in prevalence between nonalcoholic steatohepatitis (NASH) patients and NAFLD patients, while the former two types were higher than the patients infected with HBV. Both NASH and NAFLD patients had significant higher prevalence of increased glucose, over weight /obese, hypertension and hyper-triglyceridemia than that of chronic HBV patients. Proportion of low HDL- C among NASH patients

Table 1. Baseline characters of the patients infected with chronic HBV and NAFLD patients.

Group	n	Male (n, %)	Age (years)	BMI (kg/m^2)	ALT (U/L)	AST (U/L)	GGT (U/L)
HBV patients	136	103(75.7)	34.52 ± 9.97	22.63 ± 3.62	135.82 ± 258.41	76.54 ±133.37	49.54 ± 48.7
NAFLD	110	86(78.2)	37.43 ± 10.51	26.35 ± 3.38	112.63 ±104.21	61.99 ± 49.42	99.53 ±130.37
t/χ2		0.002	-2.218	-8.270	0.955	1.177	-3.810
P value		0.963	0.027	0.000	0.341	0.241	0.000

FBG (mmol/L)	TG (mmol/L)	TC (mmol/L)	HDL-C (mmol/L)	UA (μmol/L)	Steatosis (>30%)	Inflammation (≥G2)	Fibrosis (≥S2)
5.04 ± 0.56	1.85 ± 1.5	3.95 ± 1.49	1.31 ± 0.37	340.61 ± 88.05	8(5.9)	55(40.4)	71(52.2)
5.46 ± 1.27	2.24 ± 1.68	5.06 ± 1.24	1.2 ± 0.32	401.45 ± 90.96	40(36.4)	38(34.5)	41(37.3)
-3.226	-1.87	-6.404	2.512	-5.310	35.977	0.899	5.468
0.002	0.063	0.000	0.013	0.000	0.000	0.343	0.019

BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate transaminase; GGT: γ-glutamyltransferase; FBG fasting blood glucose; TG: triglyceride; TC: total cholesterol; HDL-C: HDL cholesterol; UA:uric acid.

Table 2. Prevalence and components of metabolic syndrome compared between chronic HBV patients and NAFLD patients (n,%).

Group	n	MS	FBG≥5.6 mmol/L	BMI≥25 kg/m^2	Bp≥135/85 mm Hg	TG≥1.7 mmol/L	HDL-C<1.03/1.29 mmol/L (male/female)
HBV patients	136	16(11.8)	18(13.2)	29(21.3)	12(8.8)	46(33.8)	31(22.8)
NAFL	45	18(40)	14(31.1)	28(62.2)	19 (42.2)	25(55.6)	10(22.2)
NASH	65	36(55.4)	27(41.5)	44(67.7)	32 (49.2)	48(73.8)	20(30.8)
χ^2		44.710	20.859	49.269	45.670	29.346	1.696
P Value		0.000	0.000	0.000	0.000	0.000	0.428

MS: metabolic syndrome, FBG: fasting blood glucose, BP: blood pressure; TG: triglyceride, HDL-C: HDL cholesterol; NAFL: non-alcoholic fatty liver, NASH: non-alcoholic steatohepatitis.

was lower than the other two subgroups, but had no statistic significance (Table 2).

Analysis of the relative factors which affect the liver fibrosis in chronic HBV and NAFLD patients revealed that the prevalence of metabolic syndrome in chronic HBV patients with liver fibrosis stage $S_{0\sim1}$ and $S_{2\sim4}$ were 3.1 and 19.7%, respectively (χ^2=9.053, P < 0.01), and the individuals suffered from more severe liver fibrosis had higher prevalence, BMI, aspartate transaminase, γ-glutamyltransferase and severity of inflammation (≥G2) (χ^2/t=9.053, -2.457, -2.379,-4.845, 66.346; P < 0.05 for all). However, there were no significant relationship between sex, age, alanine aminotransferase, total cholesterol, fasting glucose, uric acid and hepatic steatosis and liver fibrosis degrees (P > 0.05). On the other hand, the prevalence of metabolic syndrome in NAFLD patients with liver fibrosis stage $S_{0\sim1}$ and $S_{2\sim4}$ were detected as 36.2 and 70.7%, respectively (χ^2=3.694, P < 0.01). The individuals with obvious liver fibrosis had higher alanine aminotransferase, aspartate transaminase, γ-glutamyltransferase and severity of inflammation (≥G2) (χ^2/t=3.662, 3.863, 2.478, 61.013; P < 0.05 for all) but showed no significant correlation between sex, age, total cholesterol, triglyceride level, fasting glucose, uric acid, hepatic steatosis and liver fibrosis stage(P > 0.05 for all) (Table 3).

DISSCUSSION

Through 136 chronic HBV patients and 110 NAFLD patients liver biopsy, we found that metabolic syndrome could enhance the risk to develop liver fibrosis significant, and the prevalence of metabolic syndrome in NAFLD patients was significant higher than the chronic HBV patients, which consisted with recent research (Tsochatzis et al., 2008). Metabolic syndrome was related with the severity of liver fibrosis regardless of chronic HBV patients or NAFLD patients. However, HBeAg positive patients were excluded from the HBV group, and the HBV patients had not been separated from HCV patients, which lead the results inconvincible on the connection between HBV infection and metabolic syndrome (Tsochatzis et al., 2008). An epidemic survey conducted in USA showed that among chronic HCV patients the prevalence of metabolic syndrome as well as

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Table 3. Association between metabolic syndrome with the severity of liver fibrosis in patients with chronic viral hepatitis B infection or non-alcoholic fatty liver disease.

Group		n	MS (n, %)	Male (n, %)	Age (years)	BMI (kg/m^2)	ALT (U/L)	AST (U/L)
Chronic HBV patients	S0-1	65	2(3.1)	47(72.3)	34.09 ± 10.02	21.86 ± 2.85	102.49± 245.22	49.48± 63.55
	S2-4	71	14(19.7)	56(78.9)	34.92 ± 9.98	23.34 ± 4.1	162.34± 268.01	101.32± 171.20
t/χ^2			9.053	0.796	-0.480	-2.457	-1.445	-2.379
P value			0.003	0.372	0.632	0.015	0.151	0.019
NAFLD	S0-1	69	25(36.2)	54(78.3)	37.55 ± 9.03	26.13 ± 3.43	81.51± 58.62	46.61± 28.24
	S2-4	41	29(70.7)	32(78)	37.22 ± 12.75	26.74 ± 3.29	165 ± 138.81	87.88± 64.86
t/χ^2			3.694	0.001	-0.146	0.914	3.662	3.863
P value			0.000	0.979	0.884	0.363	0.001	0.000

GGT (U/ L)	FBG (mmol/L)	TG (mmol/L)	TC (mmol/L)	HDL-C (mmol/L)	UA (μmol/L)	Steatosis>30%	Inflammation ≥G2	GGT (U/ L)
30.43± 26.99	5.06 ± 0.58	1.84 ± 1.48	3.98 ± 1.52	1.36 ± 0.31	339.77 ± 92.11	4(6.2)	3(4.6)	30.43± 26.99
67.29± 57.14	5.01 ± 0.54	1.87 ± 1.53	3.92 ± 1.47	1.27 ± 0.42	341.38 ± 84.82	4(5.6)	52(73.2)	67.29± 57.14
-4.845	0.483	-0.139	0.221	1.313	-0.106	0.017	66.346	-4.845
0.000	0.630	0.889	0.825	0.192	0.916	1.000	0.000	0.000
71.65± 69.67	5.37 ± 1.30	2.16 ± 2.02	5.07 ± 1.37	1.17 ± 0.26	410.23 ± 87.48	26(37.7)	5(7.2)	71.65± 69.67
146.44± 185.66	5.60 ± 1.23	2.36 ± 0.88	5.06 ± 1.01	1.25 ± 0.39	386.68 ± 95.82	14(34.1)	33(80.5)	146.44± 185.66
2.478	0.927	0.599	-0.051	1.314	-1.317	0.139	61.013	2.478
0.017	0.356	0.551	0.959	0.192	0.191	0.709	0.000	0.017

MS: metabolic syndrome, BMI: body mass index, ALT: alanine aminotransferase, AST: aspartate transaminase, GGT: γ -glutamyltransferase, FBG: fasting blood glucose, TG: triglyceride, TC: total cholesterol, HDL-C: HDL cholesterol, UA: uric acid.

other components increased significantly (Shaheen et al., 2007). Some studies also indicated that the prevalence of metabolic syndrome in chronic HBV patients was lower than that of chronic HCV patients, but similar to healthy population. Some researchers proposed that the prevalence of metabolic syndrome was lower in HBV patients based on the probable mechanism that HBV infection interfered the lipid metabolism in hepatocytes which caused the decrease of serum triglyceride level (Imazeki et al., 2008; Jan et al., 2006; Luo et al., 2007). Whereas, a study from Hong Kong revealed that the appearance of metabolic syndrome could increase the risk to develop hepatocirrhosis in chronic HBV patients, and had direct correlation with the increase of the components (Wong et al., 2009). Our study showed the prevalence of metabolic syndrome in NAFLD patients was 49.1%, among which the subgroup with serious liver fibrosis was even higher. NAFLD is commonly considered as the manifestation of metabolic syndrome located in liver, and its presence could largely raise the risk of diabetes, cardiovascular disease and hepatocirrhosis due to the possible mechanism that the hyper-insulinemia and hyper-glycemia accompanied with metabolic syndrome would stimulate hepatic satellite cells activity to release the connective tissue growth factor and extracellular matrix (Paradis et al., 2001). Once fat began to deposit, the liver would function as visceral adipose tissue to secrete multiple adipocytokines, enhance reactive oxygen, cause oxidative stress response and lipid peroxidation damage and stimulate the activation of hepatic satellite cell to become the corresponding factor involved in other types of hepatic fibrosis (Asselah et al., 2006). Our findings indicated whether HBV or NAFLD patients, metabolic syndrome instead

of fatty degeneration were related with the severity of liver fibrosis. Insulin resistance was presumed as the major cause of liver fibrosis, even happened far more common in HCV patients than HBV patients (Imazeki et al., 2008).

The prevalence of metabolic syndrome in HBV patients was 11.8% in our study, which was agreement with the data of HBV patients in Hong Kong (13%) and 35 to 74 years old adults in South of China (11.5%) (Gu et al., 2005; Wong et al., 2009). Some researchers showed that the prevalence of metabolic syndrome in China increased significantly, with the number as 23.5% in city area and 14.7% in country according to the IDF diagnostic criteria (Gu et al., 2005). In the meantime, the percentage of HBsAg in China was even mounted to 7.18% made it a med-high endemic area. The synergistic effect of metabolic syndrome for liver fibrosis in HBV patients focuses us to pay attention to the early stage and processing in time for metabolic syndrome. Beside the treatment, the chronic HBV patients also need to improve their life style to control the body weight to reduce the occurrence of metabolic syndrome. The HBV patients suffered from metabolic syndrome should take hypoglycemic agents, antihypertensive drugs and lipid-regulation drug to slow down the progress of liver disease. For those patients not respond well to anti-viral therapy, the improvement of metabolic syndrome might be helpful to enhance the response rate.

Nevertheless, there were still some limits existed in our study, like only 70 cases with metabolic syndrome had been recruited, serum insulin, HOMA-IR and waist determinations had not been measured in all the patients which lead to an uncompleted evaluation of insulin resistance and the effects of central obesity in the progress of liver fibrosis. Future studies are warranted to extend the recruited population to assess the relationship between metabolic syndrome and different liver fibrosis (HBV or NASH) in chronic HBV patients. It would also be of great interests to know the effects and the mechanism of metabolic syndrome in the development of liver fibrosis or hepatocirrhosis from chronic HBV or NAFLD, as well as the influence of insulin in liver fibrosis by longitudinal study.

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