Original Article

Prevalence of Insulin Resistance in Thai Patients with Chronic Hepatitis C

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ABSTRACT

Objectives: To estimate the prevalence of insulin resistance (IR) among Thai chronic hepatitis C patients with various HCV genotype.

Methods: Twenty seven patients met the conditions for enrollment. Insulin resistance was determined with the homeostasis model assessment insulin resistance (HOMA-IR) equation, defined IR by HOMA-IR ≥ 2. The degree of necroinflammatory activity, and steatosis as well as fibrosis stage in liver biopsy specimens were scored. The data analyzed with SPSS 11.5 for Windows.

Results: The prevalence of IR as defined by HOMA-IR ≥ 2 was 77.8% (21/27) among patients with HCV infection. Eighty-eight percent of HCV genotype 1 patients and 71.4% of HCV genotype 3 patients had IR.

Conclusion: The prevalence of insulin resistance in HCV infected patients in this study was 77.8%, and it was more common in genotype 1. No significant difference was found between insulin resistance and hepatic steatosis, or hepatic fibrosis in HCV infected patients.

Key words : Chronic hepatitis C, Hepatitis C virus, Insulin resistance, HOMA-IR

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INTRODUCTION

Chronic hepatitis C infection affects over 170 million people worldwide, with 3 to 4 million persons newly infected each year.[1,2] The estimated prevalence of hepatitis C virus (HCV) infection in South-East Asian countries is 2.15%.[1,2] The prevalence of HCV infection among healthy blood donors in Thailand is about 1.8 million people, ranging from 1% in the southern region to 5% in northern Thailand.[1,2]

HCV infection is a major cause of chronic liver injury and can progress to liver cirrhosis and hepatocellular carcinoma.[3-7] Hepatic steatosis is a common feature in HCV patients as observed in alcoholic steatohepatitis (ALS) and non-alcoholic steatohepatitis (NASH). The pathophysiology of hepatic steatosis is related to metabolic syndrome, which is characterized by insulin resistance (IR) and hyperinsulinemia.[8,9]

Recent studies have found HCV infection to be associated with an increased risk of insulin resistance, specially in HCV genotypes 1 and 4.[10,11] Interestingly,

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only 22% of patients with genotypes 2 or 3 hepatitis C virus infection had insulin resistance whereas 40.1% of patients infected with genotypes 1 or 4 had the evidence of insulin resistance.[12] Insulin resistance is associated with the progression of liver disease as well as a decreased responsiveness to therapy with pegylated interferon and ribavirin.[11-15] Moreover, some findings suggest that insulin resistance is associated with liver fibrosis and may promote progression of liver fibrosis in patients with chronic hepatitis C.

There is no information about the prevalence of insulin resistance in Thai patients with chronic hepatitis C. We therefore conducted the study to estimate the prevalence of insulin resistance among Thai chronic hepatitis C patients with various HCV genotypes.

METHODS

Patients

The patient population was naïve HCV infection patients who were older than 18-year old and were seen at the Liver Clinic of Songklanagarind Hospital between December 2007 and December 2008. All participants agreed to sign the consent form. This study was approved by the Ethics Committee of Prince of Songkla University. The HCV infections in the participant were diagnosed by the positive result of anti-HCV testing and detectable HCV RNA in serum. Patients were excluded if there were diabetic, or pregnant, if they had decompensated liver cirrhosis (Child-Pugh score of B or C) or other causes of liver disease such as Hepatitis B, HIV, autoimmune liver disease, Wilson's disease, hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, α_1-antitrypsin deficiency or drug induced liver disease, if they were receiving medication which could affect insulin resistance, e.g, metformin, or drugs of the thiazolidinedione group, or other medications which can induce hepatic steatosis such as corticosteroids, valpoic acid, amiodarone, tamoxifen, or if they had any history of alcohol drinking more than 30 gm per day within 6 months prior to the study. Characteristics such as age, sex, risk factors or route of transmission were recorded.

Laboratory and imaging

The patients were asked to fast for 8 hours and venous blood was then drawn for the measurement of plasma glucose, insulin, liver function test, HCV-RNA viral load, HCV genotype, and lipid profiles. All patients underwent to perform hepatobiliary ultrasonography.

Insulin resistance was determined using the homeostasis model assessment insulin resistance (HOMA-IR) equation;

HOMA-IR equation = [fasting insulinemia (μU/ml.) × fasting glycaemia (mmol/L)] / 22.5

In previous reports a HOMA-IR < 2 has been considered "completely" normal and describes as the insulin resistance if HOMA-IR was more than or equal 2.[10]

Histopathology

The degree of necroinflammatory activity and fibrosis stage in the liver biopsy specimens were scored as described by the Knodell score or histologic activity index (HAI), by a hepatopathologist blinded to the clinical data.

Portal inflammation was scored as follows: score 0 = no portal inflammation; score 1 = mild portal inflammation; score 3 = moderate portal inflammation, and score 4 = marked portal inflammation.

Fibrosis was scored as follows: F0 = no fibrosis; F1 = enlarged fibrotic portal tracts; F2 = peri-portal septa; F3 = portal-portal septa, but no obvious cirrhosis; and F4 = probable or definite cirrhosis.

The degree of hepatic steatosis was scored as follows: grade 0 = no hepatic steatosis; grade 1 = hepatic steatosis up to 33%; grade 2 = hepatic steatosis 33-66%; grade 3 = hepatic steatosis more than 66%.[16]

Statistical Methods

All the data were expressed as mean ± SD, unless otherwise indicated. The relationship between any two variables was analyzed by standard correlation analysis conducted using the program SPSS 11.5 for Windows. The prevalence of insulin resistance in chronic hepatitis C patients was calculated by the number of patients who were HOMA-IR ≥ 2 minus the total number of patients in the study, and using chi-square and student T-test to determine the relation of the data. *P*-values < 0.05 were considered to be significant.

RESULTS

Patient characteristics

There were a total of 80 HCV-infected patients who visited the Liver Clinic of Songklanagarind Hos-

pital between December 2007 and December 2008. Of these, 27 patients met our criteria and signed their written consent form to be included in the study.

The baseline characteristics of the 27 patients are shown in Table 1. Among of them 77.8% were male, the mean age was 47.2 ± 12.5 years, the mean AST was 83.1 ± 66.7 IU/L, and the mean ALT was 82.2 ± 60.9 IU/L. The HCV genotype of the patients could be determined in only 23 patients; eight (34.8%) patients were genotype 1, 14 (60.9%) patients were genotype 3, and one (4.3%) genotype 6. The mean viral load of HCV-RNA was 2.235 ± 3.492 ($\times 10^6$) IU/ml.

Table 1. Clinical and biochemical characteristics of patients of HCV-infectied patients.

	N	Mean ± SD
Age (years)	27	47.2 ± 12.5
Sex (M : F)	27	21 : 6
Genotype (1 : 3 : 6)	23	8 : 14 : 1
AST (U/L)	27	83.1 ± 66.7
ALT (U/L)	27	82.3 ± 60.9
ALP (U/L)	27	95.2 ± 42.2
Albumin (gm/dL)	27	4.2 ± 0.6
FBS (mmol/L)	27	5.4 ± 0.7
Fasting insulin (μU/mL)	27	19.3 ± 15.6
HOMA-IR	27	4.9 ± 4.6
HCV-RNA ($\times 10^6$ IU/ml)	23	2.235 ± 3.492
Cholesteral (mg/dL)	20	159.5 ± 9.0
TG (mg/dL)	20	131.9 ± 35.7
SI (μmol/L)	25	20.3 ± 187.9
TIBC (μmol/L)	25	59.9 ± 7.1
Ceruloplasmin (mg%)	25	24.7 ± 12.9

Data are expressed as mean ± SD. HOMA-IR, homeostasis model assessment of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, Alfaphetoprotein; FBS, fasting blood sugar; TG, triglyceride; SI, serum iron; TIBC, total iron binding capacity

Table 2. Homeostasis model assessment insulin resistance in HCV-infected patients.

HOMA-IR	Number of patient
< 2	6 (22.2%)
≥ 2	21 (77.8%)

Prevalence of insulin resistance

The mean HOMA-IR level of the patients was 4.9 ± 4.6. Of 27 patients, 21 (77.8%) patients had insulin resistance as defined by HOMA-IR ≥ 2 (Table 2). Among the group of patients who had insulin resistance, HCV genotyping was performed in 18 patients, with the results that genotype 1 was found in seven patients(38.9%), genotype 3 in ten patients (55.6%), and genotype 6 in one patient (5.5%).(Table 3). HCV genotype 1 patients had insulin resistance of 87.5% and HCV genotype 3 patients had insulin resistance of 71.4%.

Liver biopsy findings

Twelve patients (44.4%) consented to have a liver biopsy. The distribution of the histopathological scoring of the portal inflammatory activity in the liver biopsy specimens was as follows: score 1, one (8.3%) patient; score 3, nine (75.0%) patients and score 4, two (16.7%) patients. None of the patients had a score 0 of portal inflammation. The distribution of the severity of fibrosis was as follows: absent in six (50.0%) patients; stage 1 in three (25.0%) patients; stage 3 in two (16.7%) patients; stage 4 or liver cirrhosis in one (8.3%) patient. The distribution of the severity of hepatic steatosis was as follows: grade 1 in eight (66.7%); grade 2 in three (25.0%) and grade 3 in one (8.3%) (Table 4).

Insulin resistance and histopathologic features

Among the group of patients who had insulin resistance, liver histology was performed in 8 patients. The portal inflammatory activity was as follows: score 1 in one (12.5%) patient; score 3 in five (62.5%) patients, and score 4 in two (25.0%) patients. The distri-

Table 3. Correlation between HOMA-IR and HCV genotypes.

HOMA-IR	N	Number of patients		
		Genotype 1	Genotype 3	Genotype 6
< 2	5	1	4	0
≥ 2	18	7	10	1
Total	**23**	**8**	**14**	**1**

bution of the severity of fibrosis was as follows: no significant fibrosis (F0-2) in six (75.0%) patients; significant fibrosis (F3-4) in two (25.0%) patients (Table 5). The severity of hepatic steatosis in patients who had insulin resistance was as follows: grade 1 in six (75.0%), and grade 2 in two (25.0%). None of the patients had hepatic steatosis grade 3. (Table 6)

Table 4. Histopathological grading in the liver biopsy specimens.

Histopathologic grading	Number of patients
Portal inflammation	
Score 0	0
Score 1	1
Score 3	9
Score 4	2
Fibrosis index	
F0	6
F1	0
F2	3
F3	2
F4	1
Hepatic steatosis	
Grade 0	0
Grade 1	8
Grade 2	3
Grade 3	1

DISCUSSION

The gold standard for *in vivo* measurement of insulin resistance is the euglycemic hyperinsulinemic clamp technique.[8] Considering this technique can induce severe hypoglycemia, particularly in cirrhotic patients and is also expensive, labor-intensive, and uncomfortable for practical use in clinical medicine, we then used the homeostasis model assessment for insulin resistance (HOMA-IR) to determine the degree of IR in the subjects based on fasting blood glucose and plasma insulin levels. HOMA-IR has been validated in comparison with the euglycemic/hyperinsulinemic clamp technique in both diabetic and non-diabetic patients.[17] In previous reports a HOMA < 2 has been considered "completely" normal and describes as the insulin resistance if HOMA-IR was more than or equal 2.[10]

The prevalence of insulin resistance in HCV infected patients in the present study was 77.8%, which was higher than those in previous studies. Recently, several groups demonstrated that HCV infection was associated with an increased risk of insulin resistance, particularly in patients with HCV genotypes 1 and 4.[10,11] Hui *et al*[12] found that HCV patients with genotypes 1 or 4 had IR of 40.1%, and those with genotypes 2 or 3 had IR of 22%. In the present study, the frequency of insulin resistance in HCV patients with genotype 1 was 87.5% and in HCV patients with genotype 3 was 71.4%. In previous studies, hepatic steato-

Table 5. Correlation between HOMA-IR and hepatic fibrosis.

HOMA-IR	N	Number of patients	
		No significant fibrosis (F0, F1, F2)	Significant fibrosis (F3, F4)
< 2	4	3	1
≥ 2	8	6	2
Total	**12**	**9**	**3**

Table 6. Correlation between HOMA-IR and hepatic steatosis.

HOMA-IR	N	Number of patients of hepatic steatosis		
		Grade 1	Grade 2	Grade 3
< 2	4	2	1	1
≥ 2	8	6	2	0
Total	**12**	**8**	**3**	**1**

sis was found to be a common feature of HCV infection particularly in HCV genotype 3. In those studies, HCV infected patients who had insulin resistance were associated with an increased risk for hepatic steatosis and hepatic fibrosis.[18] In the present study, there were no significant difference between insulin resistance and hepatic steatosis or hepatic fibrosis among HCV patients. The discordant results might be due to the small sample size in the short period of enrollment in our study.

In conclusion, the prevalence of insulin resistance in HCV infected patients in the present study was 77.8% and was more common in genotype 1. No significant difference between insulin resistance and hepatic steatosis or hepatic fibrosis was found in HCV infected patients.

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