Original Article

THAI J GASTROENTEROL 2007
Vol. 8 No. 2
May - Aug. 2007

Association of Cytochrome P450 2E1 and Insulin Resistance with Hepatic Steatosis in Chronic Viral Hepatitis

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ABSTRACT

Background: There is an increase in prevalence of hepatic steatosis in chronic viral hepatitis B and C. There were reports that hepatic steatosis impaired response of chronic hepatitis C treatment and developed more fibrosis. Insulin resistance was reported to be associated with hepatic steatosis. Cytochrome P450 2E1 also had shown some associations with steatosis of liver tissue in in vitro study.

Aim: To determine an association of hepatic steatosis with cytochrome P450 2E1 activity and insulin resistance.

Methods: We compared cytochrome P450 2E1 activity and insulin resistance between patients with and without steatosis determined by liver histopathology. All patients were admitted for a liver biopsy before starting treatment for chronic viral hepatitis.

Results: Nineteen cases of chronic hepatitis B and 25 cases of chronic hepatitis C joined our study. None of our patients had metabolic syndrome. The mean body mass index was 22.84 ± 2.90 kg/m^2. Forty-two percent of chronic hepatitis B and thirty-six percent of chronic hepatitis C had steatosis in liver histopathology. There was no difference in cytochrome P450 2E1 activity and insulin resistance between the patients with and without hepatic steatosis nor between hepatitis B and C. There was also no significant difference in HAI score and fibrosis score of liver tissue between patients with and without hepatic steatosis.

Conclusions: The cytochrome P450 2E1 activity and insulin resistance may not be associated with hepatic steatosis in patients who had low risk of metabolic syndrome. However, liver histopathology had a dynamic process. Cross-sectional study may not entirely explain the pathogenesis of hepatic steatosis in chronic viral hepatitis.

Key words : Insulin resistance, steatosis, hepatitis, cytochrome P450 2E1

[Thai J Gastroenterol 2007; 8(2): 65-72]

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INTRODUCTION

Chronic viral hepatitis is one of the common diseases especially in Thailand. We usually perform liver biopsy before treatment and find steatosis in the liver tissue. From international series, the prevalence of steatosis was around 27-51% in patients with chronic hepatitis B and 31-72% in patients with chronic hepatitis C[1]. There was no accurate data about prevalence of steatosis in chronic viral hepatitis in Thailand. With an experienced pathologist, we reviewed liver histopathology of the patients with chronic viral hepatitis B and C from 2004 to 2005. There were 73.17% and 66.67% of liver tissues from the patients with chronic hepatitis B and C, respectively, associated with steatosis. Varying degree of steatosis was found as shown in Figure 1.

The pathogenesis of steatosis in chronic viral hepatitis is poorly understood. In chronic hepatitis C, there were many mechanisms proposed in several literatures. Steatosis may occur based on viral and host factors. There was evidence that insulin resistance acted as the "first hit" of pathogenesis of non-alcoholic steatohepatitis (NASH) and then followed by the çsecond hité, oxidative stress[2]. Oxidative stress marker that we studied was cytochrome P450 2E1 (CYP 2E1) activity. There was an in vitro study that showed an over expression of CYP 2E1 in the liver of chronic hepatitis C patients with steatosis compared with those without steatosis[3]. Some data suggested that CYP 2E1 overexpression down regulated insulin signaling and contributed to insulin resistance[4]. We proposed that the mechanisms of steatosis of chronic viral hepatitis was similar to those of NASH.

In contrast with chronic hepatitis C, there were few data explaining pathogenesis of chronic hepatitis B. Most of them summarized that steatosis in chronic hepatitis B appeared to be a result of metabolic factors of host rather than the viral effect[5].

We studied whether of cytochrome P450 2E1 activity and insulin resistance were associated with steatosis in chronic viral hepatitis.

MATERIALS AND METHODS

Case selection

The study comprised consecutive naïve patients with chronic viral hepatitis B and C who underwent liver biopsy at King Chulalongkorn Memorial Hospital between January 2006 and January 2007. All subjects had hepatitis B surface antigen (HBsAg) or antibody against hepatitis C (anti-HCV) positive, serum alanine aminotransferase level >40 U/L, and the liver histopathology compatible with chronic hepatitis B or C. Hepatitis B DNA (HBV-DNA) more than 100,000 copies/ml for patients with positive hepatitis B e antigen (HBeAg positive) and more than 10,000 copies/ml for those with negative hepatitis B e antigen (HBeAg negative) or positive hepatitis C RNA (HCV-RNA) were qualified for this study. All patients never had any treatment of chronic hepatitis B or C.

The following conditions were excluded: diabetes mellitus, metabolic syndrome according to ATP III, body mass index greater than 30 kg/m^2, active alcohol drinking (more than 20 g/day of alcohol in the past 6 months) use medications that commonly known to induce hepatic steatosis such as corticosteroid, valproic acid, amiodarone and tamoxifen, human immunodeficiency virus (HIV) infection and other chronic liver diseases.

The study was approved by the ethics committee of Chulalongkorn University and each patient gave written informed consent to participate.

Clinical and laboratory assessment

The following data were collected at the time of

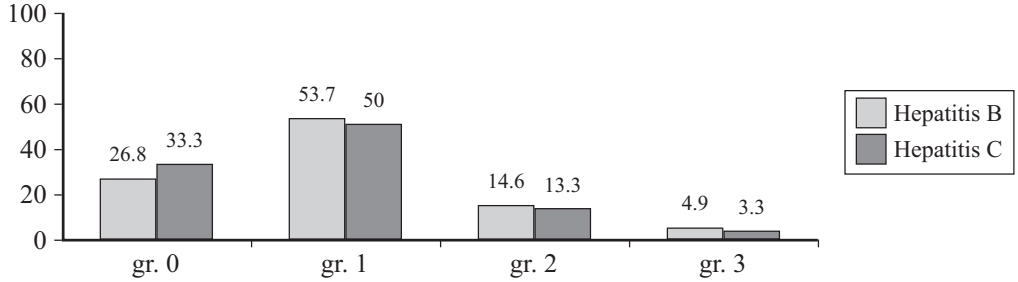

Figure 1 Different degrees of steatosis in liver pathology of patients with chronic hepatitis B and C: reviewed data from the Department of Pathology, Chulalongkorn University between 2004 and 2005.

liver biopsy: age, gender, body weight, height, waist circumference (at the level of umbilicus), hip circumference (at the maximal circumference over the buttock) and blood pressure.

After an overnight fast for 8 hours, the patients took chlorzoxazone a muscle relaxant that metabolized mainly by cytochrome P450 2E1500 mg orally. Two hours after taking chlorzoxazone, a venous blood sample was drawn to determine the serum level of alanine aminotransferase, glucose, insulin, total cholesterol, triglycerides, HDL-cholesterol, chlorzoxazone and 6-hydroxy chlorzoxazone.

Insulin resistance was determined by the homeostasis model assessment (HOMA) method by using the following equation[6].

- Insulin resistance (HOMA-IR)

$$= \frac{\text{Fasting insulin (mU/ml)} \times \text{Fasting glucose (mmol/l)}}{22.5}$$

LDL-cholesterol was calculated by the following equation.

- LDL-C

= Total cholesterol - HDL-C - (Triglycerides/5)

Cytochrome P450 2E1 activity was estimated by a proportion of 6-hydroxy chlorzoxazone to chlorzoxazone levels.

Histopathology

Standard liver biopsy was performed under ultrasound guided. All of liver tissue was evaluated by experienced gastrointestinal pathologist. The degree of necroinflammatory activity and fibrosis were scored by the histologic activity index (HAI), also known as the Knodell score. Degree of steatosis was assessed as the percentage of hepatocytes containing macrovesicular fat droplets according to Brunt's classification[7]. It was graded as 0 (no steatosis), 1 (<33% of hepatocytes affected), 2 (33-66% of hepatocytes affected), or 3 (>66% of hepatocytes affected). Then we categorized the patients into 2 groups: "no steatosis group" for grade 0 steatosis and çsteatosis groupé for grade 1, 2 and 3 steatosis.

Statistical analysis

Baseline descriptive data were expressed as means and standard deviations for continuous variables and as percentages and frequencies for categorical variables. Differences between groups were assessed using Student t-test for parametric data and Mann-Whitney test for non-parametric data. Proportional data were assessed using chi-square test.

RESULTS

There were 44 patients with chronic viral hepatitis participating in our project between January 2006 and January 2007. Thirty seven of them (84.7 %) were male. Twenty-seven cases were categorized as "no steatosis group" and 17 cases were categorized as "steatosis group". The average age of the patients was 40.98 ± 10.0 years old, ranging from 24 to 67 years old. Their body mass index (BMI) ranged from 17.04 to 29.84 kg/m2and mean BMI ± standard deviation was 22.84 ± 2.90 kg/m^2. Their mean waist-to-hip ratio ± standard deviation was 0.88 ± 0.05 with a range from 0.77 to 1.00. No significant difference of the patients'

Table 1 Patients' baseline characteristics

Parameters	Overall	No steatosis group	Steatosis group	P value
N	44	27	17	
Age (years old)	40.98 ± 10.00	40.59 ± 10.73	41.59 ± 9.01	0.75
Male	37 (84.10%)	22 (81.48%)	15 (88.24%)	0.68
Body weight (kg)	63.45 ± 11.13	61.25 ± 10.75	66.95 ± 11.13	0.43
Height (m)	1.66 ± 0.08	1.65 ± 0.09	1.68 ± 0.06	0.20
Body mass index (kg/m^2)	22.84 ± 2.90	22.30 ± 2.63	23.68 ± 3.2	0.80
Systolic BP (mmHg)	120.8 ± 12.10	119.11 ± 11.01	123.47 ± 13.55	0.42
Diastolic BP (mmHg)	72.68 ± 9.60	72.33 ± 10.02	73.24 ± 9.17	0.69
Waist circumference (cm)	83.41 ± 7.62	82.44 ± 7.44	84.94 ± 7.87	0.34
Hip circumference (cm)	94.52 ± 5.95	93.52 ± 5.94	96.12 ± 5.79	0.57
Waist to hip ratio	0.88 ± 0.05	0.88 ± 0.04	0.88 ± 0.61	0.32

Table 2 Baseline biochemical parameters of the studied patients.

Biochemical parameters	Overall	No steatosis group	Steatosis group	P value
Glucose (mg/dl)	87.61 ± 11.38	85.56 ± 7.30	90.88 ± 15.58	0.13
ALT (U/L)	112.34 ± 82.00	120.63 ± 91.97	99.16 ± 63.45	0.40
Total cholesterol (mg/dl)	181.75 ± 41.28	178.26 ± 39.72	187.29 ± 44.28	0.49
Triglycerides (mg/dl)	88.45 ± 38.43	97.56 ± 44.46	74.00 ± 19.87	0.10
HDL-cholesterol (mg/dl)	54.55 ± 13.44	52.33 ± 9.63	58.06 ± 17.71	0.52
LDL-cholesterol (mg/dl)	116.30 ± 39.94	115.46 ± 35.49	117.62 ± 47.31	0.86

baseline characteristics was detected between the 2 groups of patients with and without steatosis as shown in Table 1.

All of baseline biochemical parameters between steatosis and no steatosis groups were not significantly different as shown in Table 2.

There were 19 patients who had chronic hepatitis B and 25 patients who had chronic hepatitis C. All of them were naïve case of chronic viral hepatitis. In 19 patients with chronic hepatitis B, there were 9 cases with HBeAg-positive, 9 cases with HBeAg-negative and 1 case with unknown HBeAg status. HBV-DNA was reported over 20 million copies/ml in 8 of 19 cases (42.11%).

HCV genotyping was performed in 18 out 25 patients with chronic hepatitis C. T here were 6 cases of HCV genotype 1 and 12 cases of HCV genotype 3. HCV-RNA quantitative level more than 700,000 IU/ml was detected in 13 of 19 cases who had HCV-RNA tested.

The criteria for a diagnosis of metabolic syndrome from ATP III composed of abdominal obesity, serum triglyceride, HDL-cholesterol, fasting glucose and blood pressure are shown in Table 3. Three out of five of these criteria are needed to make a diagnosis of metabolic syndrome. None of the studied patients met 3 of 5 criteria to be diagnosed of metabolic syndrome. About half of them did not even have one of the criteria and only 5 patients had 2 of 5 criteria of metabolic syndrome. The most frequent criterion found in our patients was a high blood pressure as shown in Figure 2. No one had fasting plasma glucose more than 100 mg/dl. The number of metabolic syndrome criteria being present was not different (P = 0.997) between the groups with and without steatosis as shown in Table 4.

The hepatic steatosis grading was reviewed by

Table 3 Metabolic syndrome criteria according to ATP III.

Criteria	Details
Abdominal obesity	Waist circumference >102 cm in men Waist circumference >88 cm in women
Hypertriglyceridemia	Serum triglyceride >150 mg/dl
Low HDL	Serum HDL-C <40 mg/dl in men Serum HDL-C <50 mg/dl in women
High blood pressure	Blood pressure ≥130/85 mmHg.
High fasting glucose	Fasting glucose ≥100 mg/dl

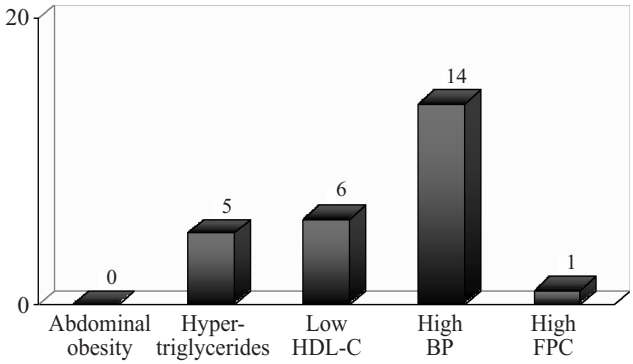

Figure 2 Number of patients in each criteria of metabolic syndrome.

Table 4 Number of patients who met metabolic syndrome criteria

Criteria of metabolic syndrome (ATP III)	Frequency	Percent
Number of criteria		
0	21	47.7
1	18	40.9
2	5	11.4

an experienced pathologist according to Brunt's classification. The grades of hepatic steatosis were further and each grade divided by type of chronic viral hepatitis as shown in Figure 4, and divided by a presence or absence of steatosis as shown in Table5.

The mean of cytochrome P450 2E1 activity of "no steatosis" group was 0.4065 ± 0.2142 and of "steatosis" group was 0.4059 ± 0.1335. There was no difference in the means of cytochrome P450 2E1 activity between "steatosis" and "no steatosis" groups (p = 0.992) as shown in Figure 5.

The mean insulin resistance (HOMA) of "no steatosis" and "steatosis" group were 1.2722 ± 1.6851 and 1.519 ± 1.2264 respectively and no statistically significant difference between the 2 groups was detected as shown in Figure 6.

There was no difference in cytochrome P450 2E1 activity and insulin resistance between hepatitis B and C as shown in Figure 7. In subgroup analysis of patients with chronic hepatitis C, there was no significant difference in cytochrome P450 2E1 activity, insulin resistance, grading of steatosis, HAI score and fibrosis score between genotype 1 and 3 (Figure 8). As in chronic hepatitis C, there was no significant difference in those factors between HBeAg-positive and HBeAg-positive chronic hepatitis B (Figure 9).

If we divided "steatosis" group into low grade of steatosis (gr. 1 steatosis) and high grade of steatosis (gr. 2 and 3 steatosis), we also could not find a difference in cytochrome P 450 2E1 activity between low grade and high grade of steatosis. There was a difference in insulin resistance between low grade and high grade of steatosis (Figure 10), with the mean of low grade of steatosis being greater than high grade of steatosis.

In 17 cases of "steatosis" group, there were 8 cases of chronic hepatitis B and 9 cases of chronic hepatitis C. A subgroup analysis of cytochrome P450 2E1 activity and insulin resistance did not show a difference between both types of chronic hepatitis as shown in Figure 11.

There was no statistically significant difference in HAI score (p = 0.74) and fibrosis score (p = 0.54) between "no steatosis" and "steatosis" groups as shown in Figure 12.

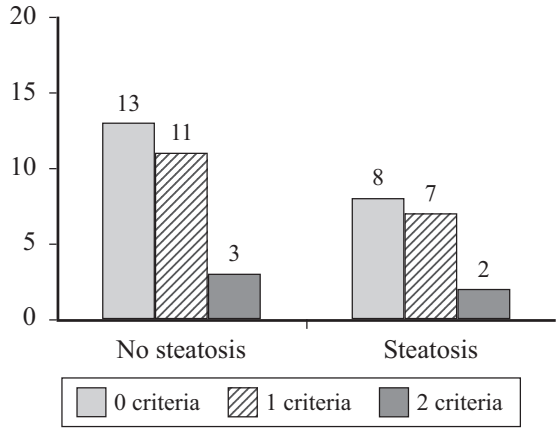

Figure 3 Number of patients who met criteria of metabolic syndrome sorted by presence or absence of steatosis.

Table 5 Presence or absence of steatosis according to type of chronic viral hepatitis.

	Viral hepatitis		Total
	Hepatitis B	Hepatitis C	
Steatosis			
No	11	16	27
Yes	8	9	17
Total	**19**	**25**	**44**

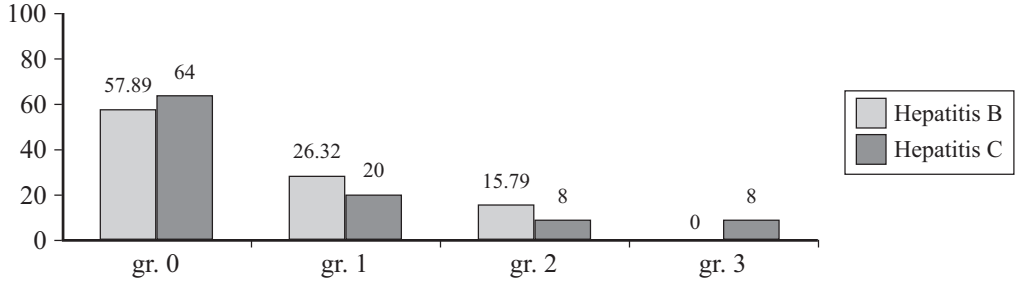

Figure 4 Grading of steatosis sorted by type of chronic hepatitis

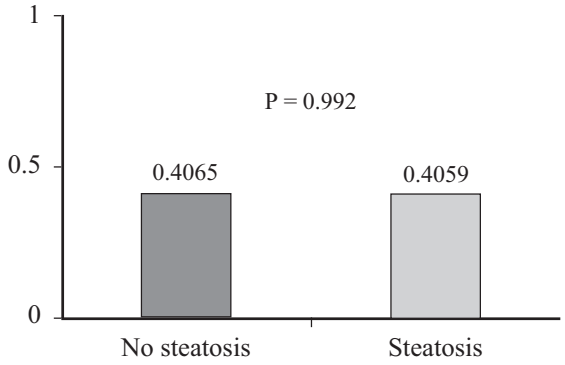

Figure 5 Cytochrome P450 2E1 activity between "no steatosis" and "steatosis" groups.

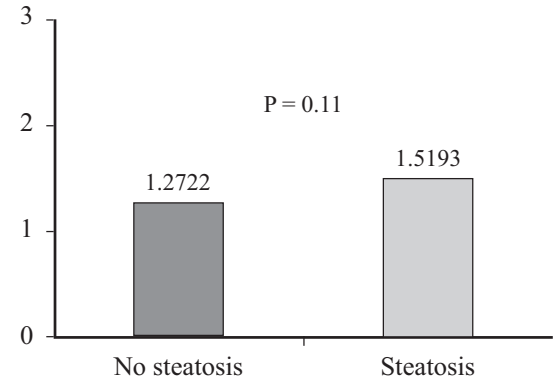

Figure 6 Insulin resistance between "no steatosis" and " steatosis" groups.

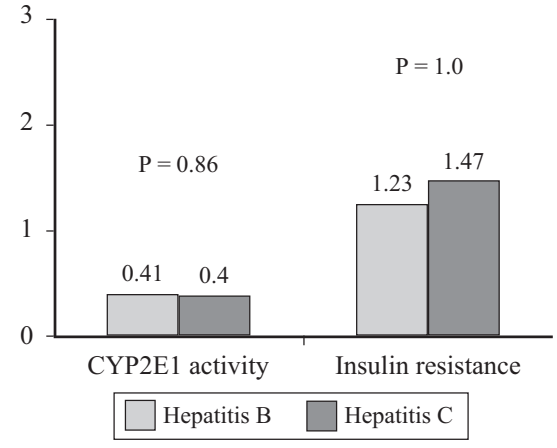

Figure 7 Cytochrome P450 2E1 activity and insulin resistance between hepatitis B and C.

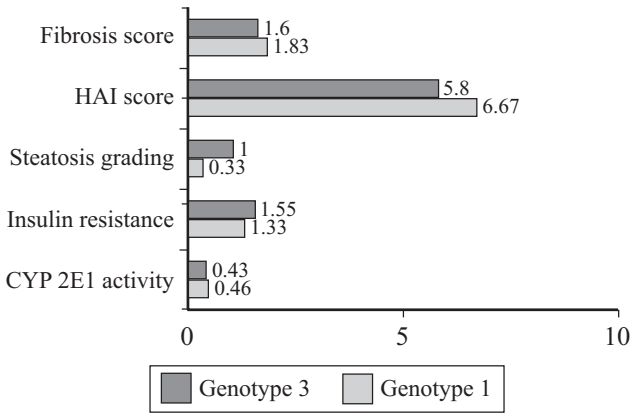

Figure 8 Fibrosis score, HAI score, steatosis grading, insulin resistance, cytochrome P450 2E1 activity in chronic hepatitis C genotype 1 and 3.

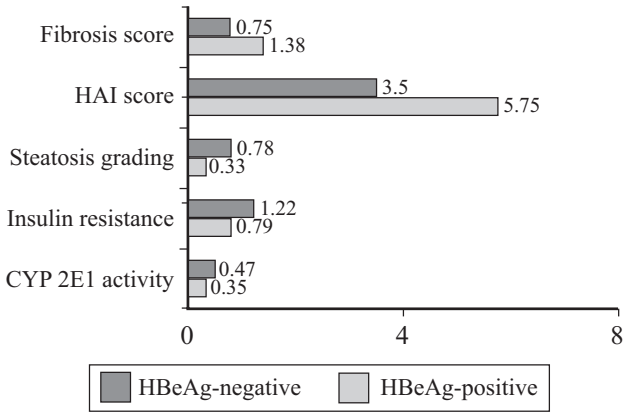

Figure 9 Fibrosis score, HAI score, steatosis grading, insulin resistance, cytochrome P450 2E1 activity in HBeAg-positive and HBeAg-negative chronic hepatitis B.

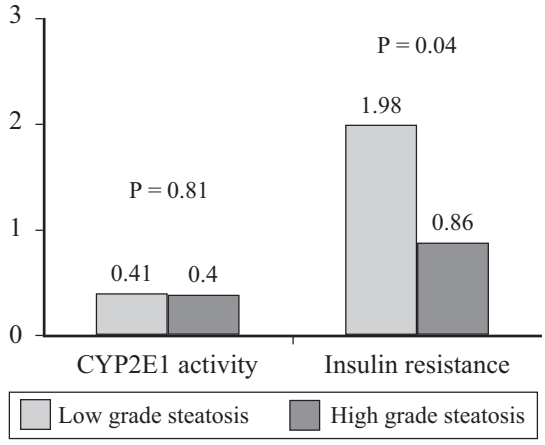

Figure 10 Cytochrome P450 2E1 activity and insulin resistance between low and high grade of steatosis.

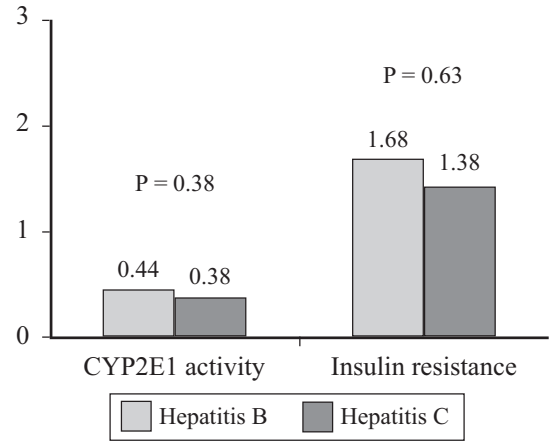

Figure 11 Cytochrome P450 2E1 activity and insulin resistance in "steatosis" group sorted by type of chronic viral hepatitis.

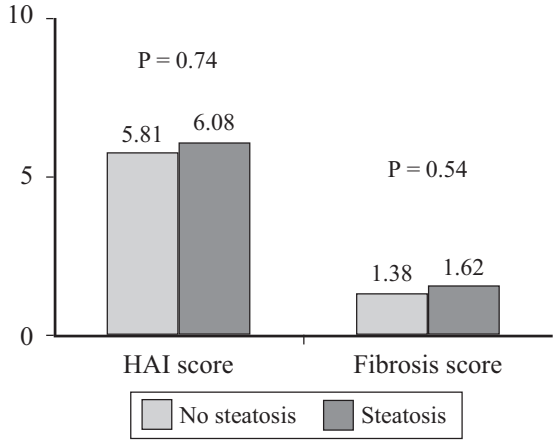

Figure 12 HAI score and fibrosis score of "no steatosis" and "steatosis" groups.

DISCUSSION

From our study, more than eighty percent of patients were men and their ages were around forty years old. There were 42.11% of chronic hepatitis B and 36% of chronic hepatitis C having steatosis in the liver histopathology. The prevalence looked different from the previously reviewed data that about 3/4 of chronic hepatitis B and 2/3 of chronic hepatitis C had steatosis. It could be explained by our study that excluded the patients with high risks to develop nonalcoholic fatty liver disease such as diabetes mellitus, metabolic syndrome, and high body mass index.

About half of the patients did not meet even one of the criteria of metabolic syndrome and only 5 patients met 2 criteria. Otherwise we also excluded active alcohol drinkers and patients who used some medications widely known as causes of fatty liver. Our patients were not obese as shown by the mean of body mass index of 22.84 ± 2.90 kg/m^2 compared with the previous studies[8,9] that their mean body mass index was over 25 kg/m^2. Therefore our study represented more accurate prevalence of steatosis associated with chronic viral hepatitis than several previous studies[5,8,9]. We assumed that steatosis developed in our patients was mainly caused by viral factor.

No difference in patients' baseline characteristics was detected between "no steatosis" and "steatosis" groups. Most of our patients had moderate degree of hepatitis which were shownd by the mean of alanine aminotransferase level around 3 times upper normal limit. Virological status showed that most of our patients had high viral load.

Steatosis impacted on several aspects of chronic viral hepatitis especially chronic hepatitis C. There was evidence that steatosis had a central role in the progression of liver fibrosis in chronic hepatitis C[10]. Steatosis appeared to negatively affect the response rate of the interferon-based treatment[11], especially the early reduction of viral load during treatment[12], even though an Italian study showed data against others[13]. Insulin resistance was postulated to be the cause of hepatic steatosis especially in hepatitis C genotype 1[14]. One study showed that the higher the degree of insulin resistance, the lower the sustained virological response rate.[15] More over, the others study showed that insulin resistance played a significant role in liver fibrosis[16,17]. Interestingly, those studies did not show the risk of metabolic syndrome despite their studied patients had higher mean body mass index and insulin resistance. Our study results could not demonstrate the difference in the means of insulin resistance between "no steatosis" and "steatosis" groups. Surprisingly, we found more insulin resistance in the subgroup of low grade of steatosis than high grade of steatosis. That result might have some false positive due to the low number of patients in the subgroup analysis. Finally, we assumed that insulin resistance was not associated with hepatic steatosis in patients with low risk of metabolic syndrome.

Cytochrome P450 2E1 activity is a representative of oxidative stress as a "second hit" in the pathogenesis of nonalcoholic steatohepatits. We could measure CYP 2E1 activity by using chlorzoxazone metabolism as a probe of in vivo testing[18]. Chlorzoxazone is

a centrally muscle relaxant that undergoes hydroxylation to form 6-hydroxy chlorzoxazone by CYP 2E1. We used high performance liquid chromatography (HPLC) technique to analyze the chlorzoxazone and 6-hydroxychlorzoxazone levels[19].

From the previous in vitro reports, CYP 2E1 overexpression was more commonly found in liver tissue from chronic hepatitis C patients with steatosis than those without steatosis[3]. The cytochrome P450 2E1 activity was also reported to be greater in the liver tissue of non-diabetic nonalcoholic steatohepatitis patients than the normal patients[20,21]. This is the first in vivo study to determine CYP 2E1 activity in chronic viral hepatitis. Our results showed no difference of CYP 2E1 activity between "no steatosis" and "steatosis" groups of chronic viral hepatitis. Additionally, in "steatosis" group, there was no difference between low grade and high grade of steatosis. We concluded that CYP 2E1 activity was not associated with hepatic steatosis by this in vivo testing. Hepatitis virus itself may induce hepatic steatosis through other mechanisms.

As the result, HAI score, fibrosis score, type of viral hepatitis (B or C), genotype of hepatitis C, HBeAg status of hepatitis B, were not associated with the presence or absence of steatosis.

In the group of patients with chronic viral hepatitis with low risk of developing metabolic syndrome, hepatic steatosis was not associated with cytochrome P450 2E1 activity and insulin resistance. However, liver pathology of chronic viral hepatitis is dynamic in its process. Our cross-sectional study alone may not explain all of the pathogenesis of steatosis of chronic viral hepatitis. More studies are required for further knowledge about pathogenesis of hepatic steatosis in chronic viral hepatitis.

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