The Role of Insulin Resistance in Diabetic Patients with Chronic Liver Disease: Preliminary Study

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ABSTRACT

Background: *The association between diabetes and chronic liver disease has been well documented. However, the mechanism remains unknown. The aim of this study was to investigate the insulin resistance in chronic liver disease and normal liver in diabetic patient.*

Method: *A total of 31 diabetic, non-alcoholic patients with multiple oral hypoglycemic drugs, either with or without lipid abnormalities were enrolled in this study. Subjects were recruited from outpatient clinic of Department of Endocrine at Dr. Sardjito Hospital, Jogjakarta, Indonesia from May-June 2004. This was a cross sectional study. Fasting insulin and glucose level, liver function test, body mass index, and the presence of fatty liver by ultrasound were examined. Insulin resistance was estimated by calculating fasting insulin and glucose plasma level as the homeostasis model assessment (HOMA) index ratio. Data was described with mean ± SD and analyzed by independent sample t-test.*

Results: *Thirty one patients were enrolled to the study, i.e. 8 patients with normal liver and 23 patients with fatty liver. Only 14 patients agreed to continue the study including 10 patients with fatty liver and 4 patients with normal liver. Mean of age was 59.1 ± 8.7 and mean value of BMI was 24.62 ± 3.05. The liver function test revealed normal results. Triglyceride, cholesterol, fasting glucose level, and HOMA index (2.77 ± 1.95 vs. 1.66 ± 1.02) in patients with fatty liver were higher than patients with normal liver. No correlation was found between fasting insulin level as well as HOMA index and mean value of BMI (obese and non-obese) as well as hypertension. There was significant correlation between triglyceride level and fasting insulin among fatty liver patients (p = 0.048; CI 95% -7.404; -0.032).*

Conclusion: *The non-alcoholic fatty liver disease in diabetic patients with normal liver enzymes and multiple oral hypoglycemic drugs appear to be related with insulin resistance and hypertriglyceridemia.*

Keywords*: fatty liver, diabetic, insulin resistance*

INTRODUCTION

Until now, the pathogenesis and therapy for patients with insulin resistance still remains unclear.[1,2] Yet, such patients have a long term risk of developing fatty liver and turn to liver cancer (hepatocellular carcinoma).[3,4] The liver of a patient with diabetes mellitus has a growing risk to become non-alcoholic fatty liver disease (NAFLD), including severe non-alcoholic steatohepatitis (NASH), which eventually will lead to liver fibrosis, cirrhosis, and 8-30% will develop into liver malignancy after 10 years period.[4,5]

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The association between diabetes mellitus and liver disease has remained uncertain whether it is caused by glucose intolerance or by the diabetes.[4,5] The pathophysiology of NAFLD also has not been fairly understood,[6] and the pathophysiology which still taken now is *the multiple-hit hypothesis* which is divided into 2 stages, i.e. stage 1 (one) a condition with insulin resistance and obesity which may cause steatosis development; and stage 2 (two) is the presence of oxidative stress which activates inflammatory response and develop into NASH. Completing stage 2, there are more stages that possibly follow due to the leptin effect which may promote insulin resistance, oxidative stress, or secretion of cytokines. The insulin resistance with or without NAFLD or DM type 2 will increase the risk of NASH and liver fibrosis and often it will develop into a chronic liver disease.[7]

This study is a preliminary study to find insulin resistance in patients with diabetes mellitus type 2 with or without chronic liver disease, as one of markers for the development of diabetes into NAFLD.

METHODS

The study subjects were 31 non-alcoholic patients with diabetes mellitus type 2, who had multiple oral hypoglycemic drug therapy, with or without serum lipid abnormalities. Subjects were recruited from outpatient clinic of Endocrine Division at Sardjito hospital, Jogjakarta, Indonesia. The study was a cross-sectional study conducted in 2 months period (May-June 2004). All patients had examinations on fasting glucose and insulin level, lipid profile (cholesterol and triglycerides level), alanine transferase (ALT) and alkali phosphatase (ALP) enzymes level as well as their measurements on body mass index. Insulin resistance was estimated by using HOMA index [fasting insulin serum level (ì U/mL) x fasting glucose plasma level (mmol/L)/22.5]. HOMA score > 2.77 was categorized as insulin resistance.[8,9]

The livers of all patients were examined by ultrasonograph to determine whether there is a feature of fatty liver and the patients had fasting condition for at least 5 hour earlier. The ultrasound diagnosis for the fatty liver was shown by bright liver manifestation (liver echo-structure was rougher than right kidney echo-structure), and NASH diagnosis was suspected if the ALT and ALP level > 2 times of upper normal limit).[7] All data were analyzed by SPSS version 11.0 with t-test for independent sample.

RESULTS

There were 31 patients enrolled in this study; i.e. 8 patients with normal liver, and 21 patients with fatty liver manifestation. However, only 14 patients agreed to continue the study, including 10 (78.6%) patients with fatty liver and 4 (21.4%) patients with normal liver. Baseline characteristics of the 14 patients are shown in table 1.

Table 1 shows no increasing mean value of ALT or ALP level. However, there is an increase of triglycerides and cholesterol level in subjects with fatty lever. Data was not analyzed by t-test since each group has different number of samples.

The subjects also had concomitant disease other than DM type 2, including hypertension, dyslipidemia and obesity (metabolic syndrome). Table 2 shows a hypertension value on 57.1%, hypercholesterolemia 71.4%, hypertriglyceridemia 57.1%, mixed hyper-cholesterolemia and triglyceridemia 35.7%. For obesity was only 42.9% and the rest was 71.4% normal. The insulin resistance estimated by HOMA index was 42.9% and the remained was 57.1% normal. Such data shows a higher number of hypertension, dyslipidemia, and obesity in patients with fatty liver than non-fatty liver. While insulin resistance was found more frequent in patients with fatty liver than the non-fatty liver. However, it has not generally showed a higher number of insulin resistance.

The association between HOMA index, insulin level, cholesterol level, and triglyceride level in subjects with fatty liver are shown on table 3. It demonstrates a significant correlation between fasting insulin level and triglyceride level (p = 0.048; 95% CI = -7.404; -0.032).

Table 1. Baseline characteristics

Variable	Mean ± SD	Non fatty liver	Fatty liver
Age (year)	57.91 ± 8.7		
History of diabetes mellitus (year)	8.54 ± 5.3		
Body mass index	24.62 ± 3.05		
Fasting glucose level (mmol/L)	8.20 ± 2.88	6.89 ± 3.96	8.56 ± 2.64
Fasting insulin (μU/mL)	7.48 ± 4.37	8.13 ± 8.70	7.30 ± 3.08
ALT (IU/L)	35.50 ± 28.03		
ALP (IU/L)	80.00 ± 30.47		
Triglyceride (mg/dL)	172.43 ± 75.97	133.33 ± 93.57	183.09 ± 71.8 8
Cholesterol (mg/dL)	228.86 ± 59.13	189.00 ± 47.79	239.73 ± 59.0 0
Liver USG		4 (21.4%)	10 (78.6%)
Sex			
Male	5 (35.7%)		
Female	9 (64.3%)		

Normal value: fasting glucose 4.2-6.4 mmol/L; ALT 0-35 IU/L ; ALP 30-120 IU/L; triglycerides <160 mg/dL; cholesterol < 200 mg/dL

Table 2. Concomitant disease of diabetes mellitus, BMI and HOMA index

Variable	Percentage	Fatty liver	Non fatty liver
Concomitant disease			
Hypertension	57.1% (8)	6	2
Dyslipidemia			
▪ hypercholesterol	71.4% (10)	9	1
▪ hypertriglycerides	57.1% (8)	7	1
▪ mixed	35.7% (5)	5	0
BMI			
Overweight (> 25)	42.9% (6)	6	0
Normal (< 25)	71.4% (8)	4	4
HOMA index			
Insulin resistance (> 2.77)	42.9% (6)	5	1
Normal (< 2.77)	57.1% (8)	5	3

Table 3. Association between HOMA index, fasting insulin level, fasting glucose level and lipid profile in subjects with fatty liver

Association	Association significance	
HOMA - BMI	p = 0.320	95% CI -1.091 ; 2.992
HOMA - cholesterol	p = 1.187	95% CI -0.900 ; 3.974
HOMA - triglycerides	p = 0.129	95% CI -3.266 ; 0.496
Fasting insulin - BMI	p = 0.541	95% CI -3.259 ; 5.802
Fasting insulin - cholesterol	p = 0.142	95% CI -1.475 ; 8.708
Fasting insulin - triglyceride	p = 0.048	95% CI -7.404 ; -0.032

DISCUSSION

In this study, the mean of age is 57.91 ± 8.7 years, 64.3% subjects are female with hypertriglyceridemia level of 228.86 ± 59.13 mg/dL, but most ALT and ALP level are normal and there is only 42.9% subjects with overweight BMI. Half of subjects (57.1%) have hypertension, a condition which is more frequent in the fatty liver group compared to the non-fatty liver group. Characteristic of patients with NAFLD are middle age, female with truncal obesity and hypertriglyceridemia.[6] Insulin resistance, hypertension and slight elevation of transamiase and alkali phosphatase enzymes are independent predictor for NASH and chronic liver disease. Insulin resistance not only has a role in lipid accumulation process in the liver but also in inflammation and necrosis of liver cells, which are in accordance with pathogenesis of NASH.[4,6,7] In diabetic patients, NAFLD is strongly correlated to insulin resistance as demonstrated by increased fasting insulin level in patients with NAFLD.[8,10] High prevalence of NAFLD in non-obese hypertension patients with normal transaminase enzyme level seems to be associated with increased insulin resistance.[11]

There is no significant difference of HOMA index in both groups, which demonstrates that insulin resistance does not appear in all subjects with bright liver ultrasonographic features. In this study, no liver biopsy was performed by investigator in all patients since liver biopsy is an invasive method and not all patients gave their consent for such treatment. Some investigators suggest liver biopsy to determine diagnosis and prognosis.[6,7] However, other investigators indicate that routine liver biopsy in patient with suspected NAFLD is still controversial considering biopsy cost and the risk. Biopsy itself can not be used to evaluate the effectiveness of therapy. Nevertheless, in general, the prognosis of NAFLD is good.[7]

This study is a preliminary study with a minimum number of subjects and was conducted in a short period. Based on minimal sample estimation for cross sectional study design, minimum number of subjects for this study is 96 subjects. As in fact, the prevalence of patients with DM type 2 is more frequent in population with mild/moderate obesity.[12] Therefore, further study in population with risk is necessary. We should also consider the possibility of increased prevalence of metabolic syndrome since the increasing level in obesity, hypertension, dyslipidemia, and hyperglycemia have a high risk of NAFLD development.[13,14]

CONCLUSION

This study shows that non-alcoholic fatty liver disease in patients with diabetes mellitus who have been treated by multiple oral hypoglycemic drug therapy has demonstrated a normal level of transaminase enzymes. Metabolic syndrome (insulin resistance, dyslipidemia, obesity and hypertension) occur in some subjects. Insulin resistance and hypertriglyceridemia may have a role on NAFLD development in diabetic patients.

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