

Transaminitis in Type II Diabetic Patients: A Study at Outpatient Clinic

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ABSTRACT

Background: Liver disease is one of the most important health problem in Thailand. Incidence of viral hepatitis, such as chronic hepatitis B and C are decreased because of primary prevention and better treatment options. Nonalcoholic fatty liver disease (NAFLD) is now a leading cause of liver disease in the new millennium especially in diabetic patients. There were studies on prevalence of NAFLD in diabetes in many countries but the actual prevalence in diabetic Thai patients is still unknown.

Objectives: The aims of the present study are (1) prevalence of liver disease in type 2 diabetes mellitus with transaminitis at outpatient clinic, Rajvithi hospital and (2) clinical characteristics of diabetic patients with biopsy proven nonalcoholic steatohepatitis (NASH).

Methods: Data collected from 391 type II diabetic patients at outpatient diabetic clinic, Rajvithi hospital. Baseline patient characteristic profile, laboratory chemistry values and liver histology were obtained for analyses on prevalence of liver disease and clinical characteristics of diabetic patients with NASH. Data were analyzed using student t-test for continuous variables and Chi-square test for categorical variables. P-value <0.05 was considered significance.

Results: Transaminitis in type II diabetic patients was found to be only 3.1% and the most common etiology was NASH. Clinical characteristics of NASH compared with the control group were demonstrated difference in statistically significant in only four variables including mean age (53.4 ± 7.8 vs 62.2 ± 11.1 years), diabetic complications (0 vs. 31%), alcohol drinking (0 vs 10%) and fasting blood sugar (200.9 ± 42.0 vs. 150.7 ± 48.5), respectively. The other variables (BMI, gender, WHR, duration of diabetes, co morbid disease and lipid profile) were not significantly different. Seven of ten patients with NASH who were proved by a liver biopsy revealed a moderate to severe degree of necroinflammatory activity and fibrotic stage 2 and 3.

Conclusion: Our findings indicated that NASH was the most common liver disease in type II diabetic patients with transaminitis, in outpatient DM clinic, Rajvithi hospital. The significant risk factors of NASH were associated with age, diabetic complications, alcohol drinking and fasting blood sugar. Additionally, most of liver histologic studies showed moderate to severe necroinflammatory activities and fibrotic stage 2 and 3, indicating a high risk for severe disease.

Key words : Transaminitis, NAFLD, Diabetes mellitus

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INTRODUCTION

Non-insulin dependent diabetes mellitus (NIDDM) is a major public health problem in Thailand. The rapid urbanization and social and economic transformation of the country have been accompanied by changes in lifestyle and an increase in incidence of the disease.

Viral hepatitis especially HBV and HCV is progressively declined in its incidence because of a better primary prevention and effective treatment options. Thus, nonalcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) are more common liver diseases in the new millennium.

A few studies⁽¹⁻⁵⁾ reported the prevalence of NAFLD between 28-55% in type II diabetic population in Iran, Saudi, and Japan. NASH which has been found to be approximately one third of NAFLD was responsible for a more severity in degree of hepatic steatosis and hepatitis that lead to chronic liver disease, eventually cirrhosis (8-10%) and some hepatocellular carcinoma⁽⁹⁻¹²⁾. This condition has been associated with the metabolic syndrome including truncal obesity, hypertension, diabetes, and hypercholesterolemia in the previous studies.^(2,4-8,13,14,20,21)

In Thailand, it has not been known an actual incidence and prevalence of nonalcoholic fatty liver disease. Therefore, if the natural history of this disease in diabetic Thai population is understood, it should help early recognition and prevention of the disease progression by prompt management.

Finally, this descriptive which study was the first to conduct in diabetic clinic, would give important information about prevalence, clinical characteristics of liver diseases for further research and the policy making of the Department of Public Health in Thailand.

PATIENTS AND METHODS

In the period of June 2006 through January 2007, all patients with diabetes mellitus in outpatient diabetic clinic, Rajvithi hospital were enrolled into the study. All subjects were Thai people aged 18 years and over. Exclusion criteria were diabetes with severe co morbid factors, such as serum creatinine level more than 3 mg/dL, underlying of active malignancy, abnormal hematologic profile (thrombocytopenia was defined as platelet count less than 50,000 cell/mm³) and pregnancy.

Informed consent in writing was obtained from

each patient. The study protocol was conformed to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the Institutional Review Board. The patients receiving therapy with insulin or oral hypoglycemic medications were considered as diabetics. In other patients, fasting plasma glucose (FPG) ≥ 126 mg/dl or 2-hr plasma glucose (PG) ≥ 200 mg/dl on more than one occasion was used for a diagnosis of DM according to the latest American Diabetes Association (ADA) criteria⁽⁸⁾. The sample size was calculated by $n = Z^2pq/d^2$. Estimated prevalence of NASH was 30 percent from the previous study; hence, the calculated sample size was 896 patients.

Initial data were collected by direct interview and OPD card reviews for history of alcohol intake (amount, duration), prescribed medicine, alternative and herbal medicine, duration of DM and its previous complications, history of intravenous drug using (IVDU) blood transfusion, prostitute contact and family history of metabolic liver disease. All patients completed physical examination, such as vital signs, body weight and height, waist and hip measurement and chronic liver stigmata.

The laboratory evaluations at the initial visit of the diabetic patients included serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), complete blood count, FPG, fasting lipid profile, and serum creatinine.

A total number of 391 patients were eligible to enter the study. All subjects were obtained. Demographic data were collected and blood sample for aspartate and alanine aminotransferase was obtained. Transaminitis was defined by the level of serum aspartate and alanine aminotransferase more than 1.5 x upper normal limit. All subjects who met the criteria for transaminitis at the first visit were advised to stop all suspicious medication to exclude drug-induced hepatitis and scheduled follow-ups at diabetic clinic for 3 and 6 months later. At 3 and 6 months, additional blood samples were obtained to determine serum AST and ALT levels to confirm transaminitis and exclude drug induced hepatitis. Complete diagnostic workup was performed to determine serum HBsAg, anti-HCV, antinuclear antibody, serum ceruloplasmin (if aged <40 years) and the ophthalmologic examination for Kayser-Fleischer rings (if aged ≥ 40 years) serum iron and total iron binding capacity for identifying other liver diseases. Establishing diagnosis of NASH or otherwise, if all laboratory tests gave negative results, was per-

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formed by informed-consent liver biopsy and abdominal ultrasonography. Criteria for grading and staging of NASH followed what used by Brunt *et al.* Patients who did not meet the criteria for transaminitis were included in the diabetic control group.

The results were expressed as mean \pm standard deviation (SD). A comparison between without NASH and with diabetic NASH groups was made using Student's t-test for continuous variables and the Chi-square for categorical variables. P-value less than was 0.05 considered significance. All statistical analyses were performed using SPSS for window software (version 11.5; SPSS Inc., Chicago, Illinois, USA).

RESULTS

The diabetic subject consisted of 391 patients (30.9% male, 69.1% female). The overall mean age was 61.9 ± 11.1 years ranging between 27 and 94 years. In 391 patients, the mean diabetic diagnostic duration was 2.7 ± 1.0 years [<1 year (9.5%), 1-5 year (39.4%), 5-10 year (24.0%) and >10 year (27.1%)] and the presence of complications was 29.9%. Diabetic complications were categorized into neuropathy (22.3%), retinopathy (10.5%) and nephropathy (9.5%). Ten percent of the subjects were alcohol drinkers, defined as alcohol consumption was greater than 30 grams/day. Current treatment and medications included aspirin (37.3%), sulfonylurea (71.1%), biguanide (67.0%), thiazolidedione (3.6%), insulin (12.3%), HMG CoA reductase inhibitor (56.0%), fibrate (8.0%) and diet control (9.5%). Comorbid diseases were also identified, including hypertension (70.8%), dyslipidemia (69.6%), cardiovascular disease (6.4%) and cerebrovascular accident (6.1%) (Table 1). Transaminitis was found in 3.1% of patients. Laboratory investigation is shown in Table 2. The prevalence of liver disease in Type 2 diabetic subjects with transaminitis was 3.2%. NASH was found in 10 (2.6%) patients, chronic hepatitis B was found in one (0.3%) patient and chronic hepatitis C was found in one (0.3%) patient. (Table 3)

There was no significant difference between diabetic control and NASH groups, regarding gender, body mass index, waist/hip ratio (WHR), duration of diabetes, co morbid disease (hypertension, dyslipidemia, cardiovascular disease and cerebrovascular accident) and all lipid profile. In the diabetic control group, mean age ($p = 0.014$), diabetic complication ($p = 0.00$) alcohol consumption ($p = 0.00$) and fasting blood sugar

Table 1 Demographic data of diabetic Thai patients

Demographic data	Overall patients
Age	61.9 ± 11.1
Gender	
Male	30.9%
Female	69.1%
Body mass index	
20-24.9	3.1%
25-29.9	39.9%
30-34.9	53.5%
35-39.9	2.8%
>40	0.8%
Waist/hip ratio	0.93 ± 0.06
Duration of diabetes	2.7 ± 1.0
<1 year	9.5%
1-5 year	39.4%
5-10 year	24.0%
>10 year	27.1%
Diabetic complications	29.9%
Retinopathy	10.5%
Neuropathy	22.3%
Nephropathy	9.5%
Alcohol amount	10.0%
<30 gm/d	7.9%
>30 gm/d	2.6%
Current medication	
Aspirin	37.3%
Diet control	9.5%
Sulfonyurea	71.1%
Biguanide	67.0%
Thiazolidedione	3.6%
Insulin	12.3%
HMG Co-A reductase	56.0%
Fibrate	8.0%
Co-morbid disease	
Hypertension	70.8%
Dyslipidemia	69.6%
CAD	6.4%
CVA or stroke	6.1%
Transaminitis ($>1.5x$)	3.1%

Table 2 Laboratory data of diabetic Thai patients

Laboratory data	Overall patients
Fasting blood sugar (mg/dL)	152.2 ± 48.9
Cholesterol (mg/dL)	211.4 ± 42.2
Triglyceride (mg/dL)	147.8 ± 56.0
HDL-C (mg/dL)	49.5 ± 14.3
LDL-C (mg/dL)	132.3 ± 41.6

($p = 0.004$) were significant by higher than NASH group (Table 4)

NASH in diabetes group was diagnosed by histopathology. There were ten histological reports from single gastrointestinal-expert pathologist. The liver histopathology revealed fat deposit [moderate (50%), severe (50%)], necroinflammatory score [mild (30%),

moderate (60%), severe (10%)], and fibrosis [stage 2 (30%), stage 3 (50%), stage 4 (20%)]. (Table 5)

DISCUSSION

The basic theme of the present study was to 1) study the prevalence of liver disease in type 2 DM with transaminitis at outpatient clinic, Rajvithi hospital and 2) identify clinical characteristics of diabetic patients with NASH. Incomplete data collection due to time constrain made it more difficult to interpret and summarize the result of this study. Additional data collection in a larger sample size is on-going in our gastroenterology unit, Rajvithi hospital.

This was the first study in Thailand showing demographic data in 391 patients from diabetic clinic. Female was predominated and the mean age was 62 years. More than half of the patients were obese by body mass index (BMI) and waist/hip ratio (WHR) criteria. Majority (70%) of the subjects had hyperten-

Table 3 Prevalence of liver disease in diabetic type 2 subjects

Disease	Prevalence (%)
NASH	10 (2.6%)
Chronic hepatitis B	1 (0.3%)
Chronic hepatitis C	1 (0.3%)
Alcoholic liver disease	-
Hemochromatosis	-
Wilson's disease	-
Autoimmune hepatitis	-
Drug-induced hepatitis	-

Table 4 Clinical characteristics of type 2 diabetic patients with and without NASH.

Characteristics	Control group	NASH group	p-value
Number	379	10	
Age	62.2 ± 11.1	53.4 ± 7.8	0.014*
Gender			0.967
Male	30.6%	30.0%	
Female	69.4%	70.0%	
Body mass index	25.8 ± 4.5	27.9 ± 3.6	0.143
Waist/hip ratio	0.93 ± 0.06	0.94 ± 0.04	0.569
Duration of diabetes	2.7 ± 0.98	2.3 ± 0.95	0.199
Diabetic complications	30.9%	0%	0.000*
Co-morbid disease			
Hypertension	71%	70.8%	0.535
Dyslipidemia	69.7%	69.6%	0.483
CAD	6.6%	6.4%	0.402
CVA or stroke	6.3%	6.1%	0.413
Alcohol	10.3%	0.0%	
<30 gm/d	8.2%	0.0%	0.000*
>30 gm/d	2.6%	0.0%	
Fasting blood sugar (mg/dL)	150.7 ± 48.5	200.9 ± 42.0	0.004*
Cholesterol (mg/dL)	210.3 ± 41.3	249.4 ± 59.9	0.070
Triglyceride (mg/dL)	147.0 ± 55.4	174.9 ± 76.8	0.121
HDL-C (mg/dL)	49.5 ± 14.4	50.1 ± 11.4	0.895
LDL-C (mg/dL)	131.4 ± 40.8	164.3 ± 61.5	0.126

*p-value <0.05 (Statistically significant)

Table 5 Histological grading and staging of NASH

Histological grading and staging	NASH patients
Fat deposit	
Mild	-
Moderate	5 (50%)
Severe	5 (50%)
Necroinflammatory score	
Mild	3 (30%)
Moderate	6 (60%)
Severe	1 (10%)
Fibrosis	
Stage 1 (perisinusoidal/cellular fibrosis)	3 (30%)
Stage 2 (periportal fibrosis)	5 (50%)
Stage 3 (bridging fibrosis)	2 (20%)
Stage 4 (cirrhosis)	-

sion and dyslipidemia. Thus, diabetic duration was less than 3 years, while one third or more had diabetic complications. Therefore, our subjects may have longer duration of diabetes before diagnosis was established. ATPIII criteria for metabolic syndrome were used for comprehensive metabolic evaluation. The previous study demonstrated that fatty liver and nonalcoholic steatohepatitis (NASH) were significantly associated with the metabolic syndrome⁽¹⁵⁻¹⁹⁾. This association had been repeatedly postulated, and was confirmed using definite criteria. NAFLD is indeed an additional feature of the metabolic syndrome, and the presence of multiple metabolic disorders is associated with more severe liver disease. At least two-third of our subjects had multiple risk factors for metabolic syndrome that more frequently related to NASH, but prevalence rate of liver disease in our diabetic patient with transaminitis was very low (2.6%) compared with the previous studies (30%) from other countries. The finding could miss lead about low prevalence of NASH in diabetes because of inadequate sample size.

The second objective was to determine the clinical characteristics of NASH in the biopsy proven group. We found four significant variables compared with diabetic control group. Mean age in NASH patients was younger than controls (54 VS. 62 years). None of NASH subjects had diabetic complications or was classified as alcohol drinker. The last significant variable is fasting blood sugar, NASH group are higher than control group (p-value = 0.004). Higher fasting blood sugar in this subject with NASH might be correlated

with more insulin resistant. But, other risk factor of metabolic syndrome, such as BMI, triglyceride, HDL-cholesterol, hypertension was not demonstrated statistically significant.

The liver biopsy revealed moderate to severe necroinflammatory and fibrotic stage 2 and 3 approach 70% of NASH cases. That severity and grading of NASH implied more severe disease and progress into cirrhosis. If type II diabetes have transaminitis from NASH are high risk group for severe disease.

In summary, this study is a part of unfinished study. Therefore, our data may not be universally representative of subjects cared in diabetes clinic. Further collection and analysis will show promising results in the future.

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