Prevalence and Profile of Fibrosis in Diabetic Patients with Non-alcoholic Fatty Liver Disease and the Associated Factors

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ABSTRAK

Latar belakang: *risiko non-alcoholic fatty liver disease (NAFLD) meningkat pada pasien dengan diabetes melitus (DM) tipe 2. Prevalensi dan faktor-faktor yang berhubungan dengan peningkatan risiko NAFLD pada populasi DM di Indonesia belum pernah diteliti. Profil derajat fibrosis pada populasi ini juga masih belum diketahui. Tujuan penelitian ini mengetahui perbedaan profil pasien DM dengan atau tanpa NAFLD serta derajat fibrosisnya.* ***Metode:*** *penelitian dikerjakan secara potong lintang terhadap pasien DM tipe 2 dewasa yang berobat di poliklinik endokrin metabolik RSCM. Pengambilan sampel dilakukan secara konsekutif. Data yang dikumpulkan mencakup usia, lama diabetes, indeks masa tubuh (IMT), lingkar pinggang, kadar HDL, trigliserida, dan HbA1C. Ultrasonografi abdomen dikerjakan pada semua pasien untuk menentukan adanya NAFLD. Pasien dengan NAFLD lalu menjalani pemeriksaan elastografi transien untuk menilai derajat fibrosis. Uji Chi Square atau Fischer's-Exact digunakan untuk analisis bivariat dan regresi logistik digunakan untuk analisis multivariat.* ***Hasil:*** *sebanyak 186 pasien dianalisis dalam studi ini, dengan 84 pasien (45,2%) terbukti mengalami NAFLD. Elastografi transien berhasil dikerjakan pada 68 pasien NAFLD, dengan 17 pasien (25,0%) terbukti mengalami fibrosis berat. Analisis univariat menunjukan perbedaan signifikan IMT (PR=1,878; 95% CI= 1,296-2,721; p<0,001) dan lingkar pinggang (PR=2,368; 95% CI= 1,117-5,017; p=0,018) antara kelompok NAFLD dan tidak. Namun pada uji multivariat, IMT merupakan satu-satunya faktor yang berbeda bermakna antara kedua kelompok (OR=2,989; 95%CI=1,625-5,499; p<0,001).* ***Kesimpulan:*** *prevalensi NAFLD pada pasien DM tipe 2 di RSCM mencapai 45,2%, dengan 25,0% di antaranya mengalami fibrosis berat. IMT merupakan satu-satunya komponen dalam studi ini yang berhubungan dengan kejadian NAFLD.*

Kata kunci: *non-alcoholic fatty liver disease (NAFLD), diabetes melitus, fibrosis.*

ABSTRACT

Background: *the risk of Non-Alcoholic Fatty Liver Disease (NAFLD) is increasing in patients with type-2 diabetes. Prevalence and factors related to the increased risk of NAFLD in diabetic patients in Indonesia has never been studied before. Data regarding the profile of fibrosis in the population has also been unknown. This study aimed to identify the difference on the profile of diabetic patients with and without NAFLD as well as the degree of fibrosis.* ***Methods:*** *the study was conducted using a cross-sectional method in type-2 diabetic patients who were treated at the outpatient clinic of endocrinology and metabolic division in Cipto Mangunkusumo Hospital. Sampling was done consecutively. Collected data comprised of age, duration of diabetes, body mass index (BMI), waist circumference, HDL, triglyceride, and HbA1C levels. Abdominal ultrasonography*

was conducted for all patients to determine the presence of NAFLD. Patients with NAFLD were subsequently underwent transient elastography in order to assess their degree of liver fibrosis. Chi-square or Fisher's-Exact tests were used for bivariate analysis and logistic regression was used for multivariate analysis. ***Results:*** *as many as 186 patients were analyzed in the study and 84 patients (45.2%) were demonstrated to have NAFLD. Transient elastography examinations were carried out in 68 patients and 17 patients (25.0%) were found with severe fibrosis. Univariate analysis showed significant differences on BMI (PR=1.878; 95%CI= 1.296-2.721; p<0.001) and waist circumference (PR=2.368; 95%CI= 1.117-5.017; p=0.018) between patients with and without NAFLD. However, the multivariate test showed that BMI was the only factor that had a significance difference between both groups (OR=2.989; 95%CI=1.625-5.499; p<0.001).* ***Conclusion:*** *prevalence of NAFLD among type-2 diabetic patients in Cipto Mangunkusumo Hospital has reached 45.2% and 25.0% among them had severe fibrosis. BMI is the only factor found to be associated with the occurrence of NAFLD.*

Keywords: *non-alcoholic fatty liver disease (NAFLD), diabetes melitus, fibrosis.*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease, characterized by steatosis or the formation of fat in the liver. In Western countries, NAFLD has been regarded as the most common form of chronic liver disease. The prevalence of NAFLD in general population of the USA is 24%-51%.[1,2] While in Indonesia, one study has revealed that fatty liver affected 30% of the population.[3] As a part of disease spectrum, NAFLD is a process which consists of 2 stages: Non-Alcoholic Fatty Liver (NAFL) and Non-Alcoholic Steatohepatitis (NASH). Ultimately about 10%-29% of patients will eventually develop risk of cirrhosis in 10 years; while 4%-27% of them will lead to hepatocellular carcinoma.[2]

The association between NAFLD and metabolic disease has been studied for decades. The available data show that the prevalence of NAFLD may reach 69% among patients with type-2 diabetes mellitus (DM); while the prevalence of diabetes mellitus in NAFLD population may reach 33-50%. Those studies were conducted in the USA, where most of the population involved is Caucasian. The prevalence of NAFLD patients with DM and obesity may reach 70%.[4]

Age, duration of DM, Body Mass Index (BMI), waist circumference, the serum levels of HbA1C, LDL, and triglyceride are factors that have been widely accepted to be affecting the NAFLD incidence in DM patients, which has been oftenly discussed in overseas studies.[5] However, there has been no data in Indonesia on the prevalence of NAFLD and its associated factors in DM population. Data about the severity of fibrosis stage in Indonesian population has been not available as well. Lack of data may lead to the lack of awareness among medical workers on the urgency of NAFLD triage in DM population. Therefore, our study was aimed to evaluate the burden of NAFLD among DM population in Indonesia.

METHODS

The study was a cross-sectional study among adult patients with type-2 diabetes mellitus, who were registered at the Endocrinology Outpatient Clinic in Cipto Mangunkusumo Hospital. Consecutive sampling was performed. Patients who had given their informed consent went through history taking and physical examination to collect data of age, duration of DM, anti-diabetic and anti-cholesterol medications, BMI, waist circumference, HDL, triglycerides and HbA1C levels. Ultrasonography was performed using the instrument of USG GE Healthcare Logiq P6. Diagnosis of NAFLD was made when increased echogenicity of liver parenchymal compared to renal cortex in the same window were found. Transient elastography examination using the instrument of Echosens Fibroscan 502 Touch was then performed in NAFLD patients to determine the degree of fibrosis including mild moderate and severe fibrosis with a limit of 9.6 kPa. The collected sample was then categorized based on the presence or absence of NAFLD as

the dependent variable and based on age (<40 or ≥40 years), duration of DM (<5 or ≥5 year), BMI (<25.0 or ≥25.0), waist circumference (<100 or ≥100 cm for male and 90 cm for female), HbA1C level (<7.0 or ≥7.0), HDL level (above 40 for male and 50 for female without medication or below 40 for male and 50 for female with or without medication) and triglycerides level (below 150 mg/dL without medication or above 150 mg /dL with or without treatment), which served as independent variables. Chi-square or Fischer's exact test was used for bivariate analysis and logistic regression was used for multivariate analysis.

By compiling data from literatures, we found that minimum sample size to evaluate the prevalence of NAFLD in DM patients was 83 subjects, while the minimum sample size to examine the factors associated with NAFLD incidence was 152 subjects.

RESULTS

We recruited 191 patients in the study. As many as 5 patients had met the exclusion criteria resulted in only 186 subjects included in data analysis. Among them, 84 patients (45.2%) in our study had been demonstrated of developing NAFLD, while 16 subjects of NAFLD patients were unable to undergo transient elastography. Most of the subjects in our study were over 40 years old with a median age of 58 years. The proportion of female to male patients was relatively balanced. Most of the patients had suffered from DM of more than 5 years, with a median of 96 months. Data of BMI showed a relatively balanced result on the proportion of obese to non-obese patients; while data of waist circumference demonstrated that there were a high proportion of patients with central obesity (83.3%). Mean waist circumference was high (94 cm). Most of the patients also showed a high level of triglycerides (83.3%) and a low level of HDL (84.4%) or they were taking medications in order to keep those parameters within the normal limits. Only 34.4% of patients had HbA1C level below 7.0% (mean value of 7.45%). Basic subject characteristics can be seen in **Table 1**.

Tabel 1. Subject's characteristics

Variables	Value
NAFLD, n (%)	
- Yes	84 (45.2)
- No	102 (54.8)
Sex, n (%)	
- Male	82 (44.1)
- Female	104 (55.9)
Age (years), n (%)	
- <40	12 (6.5)
- ≥40	174 (93.5)
BMI (kg/m^2), n (%)	
- <25	82 (44.1)
- ≥25	104 (55.9)
Waist circumference (cm), n (%)	
- Normal	31 (16.7)
- Increased	155 (83.3)
Male	
- Normal	25 (30.5)
- Increased	57 (69.5)
Female	
- Normal	6 (5.8)
- Increased	98 (94.2)
Duration of DM (months), n (%)	
- <5 years	72 (38.7)
- ≥5 years	114 (61.3)
HDL (mg/dL), n (%)	
- Normal	29 (15.6)
- Low	157 (84.4)
Male	
- Normal	16 (19.5)
- Increased	66 (80.5)
Female	51 (8-91)
- Normal	13 (12.5)
- Increased	91 (87.5)
Triglycerides (mg/dL), n (%)	
- Normal	31 (16.7)
- High	155 (83.3)
HbA1C (%), n (%)	
- <7.0	64 (34.4)
- ≥7.0	122 (65.6)
Degree of Fibrosis (in NAFLD patients)	
- F0-F2 (Mild)	51 (75.0)
- F3-F4 (Severe)	17 (25.0)

Univariate analysis has shown that there was no significant correlation on age, duration of DM, triglycerides, HDL and HbA1C levels between NAFLD patients and non-NAFLD patients. We found significant correlations only

for the BMI variable (PR=1.878; 95% CI=1.296-2.271; p<0.001) and waist circumference (PR=2.368; 95% CI=1.117-5.017; p=0.018). Complete results of univariate analysis on factors associated with NAFLD incidence in our study can be seen in **Table 2**.

The obtained results using multivariate analysis showed that BMI was the only factor associated with NAFLD incidence in DM patients with odd ratio of (OR) 2.989 and CI 1.625 - 5.499. The results of the logistic regression can be seen in **Table 3**.

To evaluate the degree of fibrosis in DM patients with NAFLD, we performed transient elastography in patients with NAFLD. As many as 16 patients were unable to undergo the test; therefore, a total of 68 patients were evaluated. Among them, there were 17 patients (25.0%) who were in severe fibrosis stage; while 51 patients (75.0%) had mild fibrosis or no fibrosis at all. The descriptions of subject characteristics based on their degree of fibrosis are shown in **Table 4**.

DISCUSSION

This study found that the prevalence of NAFLD in type-2 diabetes mellitus population was 45.2%, which was higher than the results in Hasan et al study that was conducted among general population in Indonesia (30%). However, our result is lower than the result obtained by Lesmana et al[6] (51%), which was also conducted among general population in Indonesia.[3] Our results are consistent with results of other studies, which were conducted among type-2 diabetes mellitus population. Data of Western population has demonstrated that the prevalence of NAFLD in diabetes mellitus patients may reach 69%;[1] while data from Malaysia and Nigeria have shown the rate of 49.2% and 16.7% respectively.[7,8] Different background of the subjects was assumed to affect our results compared to other studies. NAFLD was known to be associated with sedentary life style, which is primarily found in developed countries.[9]

A study among general population conducted by Lesmana et al[6] has shown that age is one of

Table 2. Analysis on factors associated with the incidence of NAFLD

Variables	non-NAFLD n (%)	NAFLD n (%)	PR (95% CI)	p
Age			1.647 (0.514-5.280)	0.395
- <40	8 (7.8)	4 (4.8)		
- ≥40	94 (92.2)	80 (95.2)		
BMI			1.878 (1.296-2.721)	<0.001
- <25	57 (55.9)	25 (29.8)		
- ≥25	45 (44.1)	59 (70.2)		
Waist Circumference			2.368 (1.117-5.017)	0.018
- Normal	23 (22.5)	8 (9.5)		
- Increased	79 (77.5)	76 (90.5)		
Duration of DM			0.737 (0.513-1.058)	0.097
- <5 years	34 (33.3)	38 (45.2)		
- ≥ 5 years	68 (66.7)	46 (54.8)		
HDL			1.830 (0.880-3.804)	0.096
- Normal	20 (19.6)	9 (80.4)		
- Low	82 (10.7)	75 (89.3)		
Triglycerides			1.304 (0.672-2.529)	0.429
- Normal	19 (18.6)	12 (14.3)		
- High	83 (81.4)	72 (85.7)		
HbA1C			1.285 (0.852-1.937)	0.226
- <7.0	39 (38.2)	25 (29.8)		
- ≥7.0	63 (61.8)	59 (70.2)		

Table 3. Logistic regression on factors associated with the incidence of NAFLD

	Variables	Significance (p)	Odd Ratio (OR)	95% CI
Initial variables in the analysis	BMI	0.019	2.283	1.146-4.708
	Waist circumference	0.396	1.536	0.571-4.130
	Duration of DM	0.123	0.603	0.318-1.147
	HDL	0.327	1.574	0.636-3.897
	HbA1C	0.116	1.702	0.877-3.302
End Result	BMI	<0.001	2.989	1.625-5.499

Table 4. The profile of subject characteristics of NAFLD patients based on the degree of fibrosis

Variables	F0-F2 (mild to moderate)	F3-F4 (severe)
Sex, n (%)		
- Male	18 (35.5)	8 (47.1)
- Female	33 (64.7)	9 (52.9)
Age (years), n (%)		
- <40	4 (7.8)	0 (0)
- ≥40	47 (92.2)	17 (100)
BMI (kg/m^2), n (%)		
- <25	13 (25.5)	5 (29.4)
- ≥25	38 (74.5)	12 (70.6)
Waist circumference (cm), n (%)		
- Normal	3 (5.9)	3 (17.6)
- Increased	48 (94.1)	14 (82.4)
Duration of DM (years), n (%)		
- <5 years	25 (49.0)	6 (35.3)
- ≥5 years	26 (51.0)	11 (64.7)
HDL (mg/dL), n (%)		
- Normal	4 (7.8)	2 (11.8)
- Low	47 (92.2)	15 (88.2)
Triglycerides (mg/dL), n (%)		
- Normal	6 (11.8)	3 (17.6)
- High	45 (88.2)	14 (82.4)
HbA1C (%), n (%)		
- <7.0	18 (35.3)	2 (11.8)
- ≥7.0	33 (64.7)	15 (88.2)

the predictors for NAFLD. Another review by Seto et al[10] has also suggested that age is one of the factors to increase the risk of NAFLD among general population in Asia. However, another study by Almobarak[11] in DM patients had shown that there was no correlation between age and NAFLD incidence. Similar results have also been found in our study in which the age has no association with the incidence of NAFLD (p=0.335). Most of patients, in both groups of NAFLD and non-NAFLD population, suffered from DM for more than 5 years; however, there was no significant difference between both groups. It indicates that the process of NAFLD is not associated with the duration of DM. The available literatures explain that the process of NAFLD might have occurred long before DM had been diagnosed.[12]

Most of the patients in our study, either those with NAFLD or without NAFLD, were found to have central obesity; however, higher incidence of obesity was found in NAFLD population (p=0.018). Nevertheless, in multivariate analysis, we found that there was larger number of obesity measured by BMI in NAFLD population compared to non-NAFLD subjects (70.2% vs. 44.1%, OR 2.989; 95% CI 1.625-5.499; p<0.001). A study by Trovato et al, which involved 532 NAFLD patients and 667 patients in the control group, has successfully shown that there was a correlation between high BMI and the incidence of NAFLD.[13] Meanwhile, a study by Wang et al has shown that the prevalence of NAFLD was increased in the group with higher BMI.[14]

Similar to central obesity, most patients in our study had similar parameters of metabolic syndrome regardless the presence or the absence of NAFLD. There was no difference found between both groups in regard to HDL, Triglyceride and HbA1C levels in our study. A similar study was performed in 2008 by Leite et al.[5] The results were also similar to ours, in which that both blood glucose control and HDL were not associated with the increased risk of NAFLD in DM patients. The most prominent NAFLD indicator in this study was BMI (OR= 7.1; 95% CI=3.0-17.0). Such finding is consistent with our study. Unlike our results, the data from DM population in Nigeria has demonstrated a correlation between NAFLD in DM with central obesity and low HDL level. On the other hand, the researchers had also found that there was no association between triglycerides level and NAFLD.[8] Another study conducted in Caucasian population with DM has shown that higher waist circumference and low level of HDL were two predictors of NAFLD in DM patients. Nevertheless, the same study has also revealed that there was no association between HbA1C and Triglyceride with NAFLD incidence.[15] The contradictive results have indicated the fact that there are a lot of unidentified factors underlying NAFLD incidence in patients with diabetes mellitus.

Results obtained from our study that shows no correlation between general parameters of metabolic syndromes and NAFLD incidence in DM patients is definitely contrary to many literatures.[6,16] In spite of that, all previous studies had been focusing on the correlation in general population instead of DM patient. If we perform the evaluation only using descriptive method, the results obtained in our study may have been consistent with previous studies, i.e. there is a high incidence rate of metabolic syndrome in NAFLD patients. If it is compared to normal population, the result would show significant difference. However, in our study, we found that the increased incidence rate of metabolic syndrome could also be found in DM patients without NAFLD. It may cause a significant difference in BMI; while not being significant in waist circumference parameter.

The mechanism that leads to disturbances of metabolic parameters in general population with NAFLD is activated by DM; therefore, the presence of NAFLD does not show different characteristics in this population. Recent literature reviews have also mentioned that there has been no study that could explain the causal correlation between metabolic syndrome and NAFLD.[17] We found a relatively high proportion of patients with central obesity (83.3%), even in the non-NAFLD population; while the proportion of patients with increased BMI was not found as high as those with increased waist circumference.

Our study found the incidence of severe fibrosis in 25% of patients with NAFLD. The rate is higher than result of a study conducted in Sudan showing that severe fibrosis only found in 14.3% of the diabetes mellitus population with NAFLD.[11] However, study to examine the degree of fibrosis in patients with NAFLD is still considered rare. The available studies are mostly conducted in general population; therefore, result of our study is one of few data that assess the degree of fibrosis performed in Type 2 DM patients.

A study by Kwok et al[18] has shown increased rate of cirrhosis as much as 20.6% in DM patients with NAFLD. The rate is lower than what our finding. However in the study, transient elastography was performed in all DM population with only 72.8% of them had

NAFLD. Patients with severe fibrosis in the study shared the same characteristics with those in our study in terms of age, duration of DM, BMI, waist circumference, HDL and HbA1C levels. The only different characteristic with our population was the triglycerides parameter.

Kwok[18] has also suggested that the increased rate of cirrhosis in type-2 DM adult population is affected by longer DM duration, higher BMI, increased ALT, increased ratio of urinary albumin: creatinin levels and low HDL levels. The overseas studies so far have not set any agreement regarding which metabolic parameter that could predict the severity of fibrosis in DM patients with NAFLD. It is also supported by the fact that neither literature could find the causality between fibrosis and metabolic syndrome.[19]

The advantages of our study were that study provides the first data of prevalence and fibrosis profile of DM population in Indonesia. Moreover, the evaluated variables in the study were those that are routinely examined in DM patients. However, the study has some limitations, which include the cross-sectional design and therefore, it cannot describe the causality and in addition, the diagnosis of NAFLD in our study was made by using USG, which is not a gold standard parameter for NAFLD diagnosis. The study has already met the minimum requirement of sample size as well as covered the accessible and target population, therefore, the internal and external validation is relatively good and the result of the study could be well-generalized.

CONCLUSION

From the study, it can be concluded that the prevalence of NAFLD in adult patients with type-2 DM who seek treatment in Cipto Mangunkusumo Hospital is 45.2% and severe fibrosis is found in 25.0% among them. BMI is the only component in our study that has shown an association with the incidence of NAFLD in type-2 DM patients. Other factors such as age, waist circumference, duration of DM, HDL, triglyceride and HbA1C levels do not show any significant association.

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