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Original Article

The influence of insulin resistance in the occurence of non-alcoholic fatty liver disease among first degree relatives of type 2 diabetes

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ABSTRACT

Background: First degree relatives (FDR) of type 2 diabetes mellitus (T2DM) predisposes individuals to have earlier metabolic and vascular disorders independent of insulin resistance (IR) such as thicker carotid intima media thickness than that of non-FDR. Non-alcoholic fatty liver disease (NAFLD) is the most commonly found chronic liver disease in T2DM which is IR dependent. Studies about NAFLD in FDR of T2DM populations are very limited and inconclusive. It is unclear whether the occurrence of NAFLD in FDR of T2DM is IR dependent or due to genetic vulnerability.
Aims: The aim of this study is to determine the association between NAFLD and FDR of T2DM.
Method and materials: A total of 118 young adults (19–39 years old) with normal glucose tolerance (59 FDR of T2DM and age-sex matched 59 non-FDR subjects) were included in this cross-sectional study. Anthropometric measurement and routine laboratory analysis (fasting blood glucose/FBG, HbA1c, lipid profile, alanine aminotransferase (ALT), aspartate transaminase (AST)) were examined. Fatty liver was diagnosed by ultrasonography (US) using standard criteria.
Results: Twenty-six (22,03%) subjects with NAFLD were detected by ultrasound with similar proportion for each group. Low HDL-C level and metabolic syndrome were found higher in FDR group ($p = 0.004$, OR 3.81, CI95 = 1.47–9,91; $p = 0.023$, OR 4.28, CI95 = 1.13–16.23). Based on logistic regression analysis, central obesity and obesity had statistically significant influence towards NAFLD.
Conclusion: The occurrence of NAFLD in FDR of T2DM was influenced by IR (central obesity and obesity).

1. Introduction

The prevalence of diabetes mellitus (DM) is increasing throughout the world [1]. According to International Diabetes Federation (IDF), Southeast Asia is the second highest area with 82 million DM patients [2]. In Indonesia, proportion of patients with DM has been increased from 5.7% with 73% undetected patients in 2007 to 6.9% with 69.9% undetected patients in 2013 [3].

There is a growing evidence that besides environmental factors, genetic factor also has an important role in the occurrence of T2DM. A family history of T2DM predisposes individuals to have diabetes due to disturbance of pancreatic beta cells dysfunction at young age and asymptomatic IR [4–6]. However, some studies have shown that genetic factor in FDR could play an important role to cause other metabolic and vascular abnormality independent of IR. Dash et al. [7] found that carotid intima media thickness in FDR of T2DM was thicker than that of non FDR group although they have normal glucose tolerance and similar BMI, degree of IR and adiposity markers. Fatty acid-binding protein (FABP), cytokine that contributed in metabolic disturbance produced by adipocyte, could be one of the reasons that could explain this condition [8,9]. Higher

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concentration of FABP in FDR DMT2 can promote palmitate-induced mitochondrial dysfunction [8,10]. Accumulating evidence indicate that hepatic mitochondrial dysfunction and oxidative stress have a significant role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) [11].

NAFLD is the most common chronic liver disease in the community [12]. The high prevalence of IR in NAFLD patients has encourage some experts to consider NAFLD as a part of metabolic syndrome [13,14]. IR induces excessive lipolysis in adipose tissue and adipogenesis in hepatocyte. When accumulation of hepatic triglyceride exceeds synthesis and excretion of very-low density lipoprotein (VLDL), fatty liver will occur [15]. NAFLD can increase the risk of cardiovascular disease, cirrhosis, liver failure, and hepatocellular carcinoma [16,17].

Studies about NAFLD in FDR of T2DM populations are very limited and inconclusive. Abdelmalek et al. [14] stated that the prevalence of NAFLD and cirrhosis in FDR of T2DM were higher than that of non FDR although the prevalence of obesity, hyperlipidemia and hypertension were similar. Adibi et al. [18] in Iran reported that FDR of T2DM had 1.83 times risk of NAFLD but affected by other covariates, in particular obesity. However, both of the research included subjects with wide age range and prediabetes. Age, sex and IR were proven to have a good correlation with the occurrence of NAFLD. Thus, both of the research couldn't show direct relationship between FDR of T2DM and NAFLD without going through IR as an intervening variable. This research aims to determine the association between NAFLD and FDR of T2DM.

2. Material and methods

2.1. Study subjects

This cross sectional study was conducted during June 2018 to September 2018 involving a total of 118 subjects. Fifty-nine subjects with FDR of T2DM and age sex matched 59 subjects with non-FDR were recruited. Sample size was calculated to detect a statistically significant difference between two proportions (95% confidence level and 80% power). Sample collection was done using consecutive sampling method. This study was conducted at the Endocrine Outpatient Clinic in RSCM in Jakarta, Indonesia. All T2DM patients were offered about their children's possibility to participate in the study consecutively. Researchers contacted the candidates and explained the procedures. Informed consents were taken for subjects who met the inclusion criteria. The inclusion criteria were men or women aged 19–40 years, normoglycemia and normotension (HbA1c <5.7%, blood pressure <140/90 mmHg). Non-medical workers in RSCM, who didn't have family history of diabetes and met the inclusion criteria same with FDR group, were enrolled in this study. Exclusion criteria for both groups were severe obesity (BMI>30 kg/m^2), alcohol consumption more than 20 g/day; smoking; have a history of coronary heart disease, heart failure, arrhythmia, anemia, stroke, transient ischemic attack, peripheral arterial disease, history of hypertension, diabetes mellitus; taking hypertension drugs, oral contraceptives or other drugs that affect lipid or glucose metabolism; have a history of liver disease, kidney disease and other chronic diseases, and has a history of acute bleeding or a history of repeated blood transfusions.

This study was approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia (0242/UN2·F1/ETIK/2018).

2.2. Measurements and laboratory assays

Weight and height measurement were examined using the calibrated “Shoenle” scales and microtoise height measuring instruments. Body mass index was calculated using the following formula: Weight (kg)/Height [2] (m^2). Obesity was defined as BMI≥25 kg/m2. Waist circumference was measured using “Butterfly” clothing meter to determine whether there is central obesity (≥80 cm in women and ≥90 cm in men, based on NCEP ATP III Asia Pacific modification criteria). Blood sample for ALT, AST, FBG and lipid profile was taken after 12 h of fasting. Serum triglyceride, LDL cholesterol (LDL-C), HDL cholesterol (HDL-C) and total cholesterol levels were examined after fasting for at least 12 h, using the Roche Cobas 501 M MPA tool with an enzymatic colorimetric method.

Fatty liver was diagnosed by transabdominal ultrasound. The echogenicity of the liver were examined by an internal medicine specialist using a B-Mode US. The examinations were carried out by blinded single operator using transducer 3,5 MHz convex-probe (E66D Eccoson). The diagnosis of NAFLD was established if the US showed increased echogenicity when compared to the renal parenchyma [13]. US is widely available and have 84.4% sensitivity and 93.6% specificity in determining fatty liver disease, thus decided to be sufficient as a mean to diagnose NAFLD in this study [19].

2.3. Statistical analysis

Analysis was done electronically using SPSS 20.0. The researcher set a two-way hypothesis and the value of α 5%, β 20%. Statistical significance was defined as p value < 0.05. Subject characteristics are shown in the table of the basic characteristics of subjects based on anthropometrics, demographics, laboratory results and compared between each subject of FDR of T2DM and those without FDR of T2DM. Numerical variables with normal distribution are displayed in the form of mean and standard deviation. For numerical data with abnormal distribution will be presented in median and minimum-maximum values. Data normality was tested using Kolmogorov-Smirnov test. Numeric variables were analysed using student t-test. The asscociation between FDR of T2DM and NAFLD will be evaluated by formula of difference between two independent proportion. Bivariate and multivariate analysis were calculated to evaluate the association between obesity; low HDL-C; hypertriglyceridemia; central obesity and NAFLD. Bivariate analysis were examined using Chi-square or Fischer test. Variables with $p < 0.25$ will be further calculated with multivariate analysis using logistic regression. The results of bivariate and multivariate analysis which are considered significant are variables with a value of $p < 0.05$.

3. Results

3.1. Subjects characteristics

During study period, there were 118 patients were included, consist of 59 patients in each group. No significant differences were found for BMI, waist circumference, waist-hip ratio, FBG, lipid profile, and liver enzymes between both groups. However, we found that the proportion of metabolic syndrome and low HDL-C were significantly higher in FDR group than that of non-FDR group (Table 1). Although we found significant statistical difference in term of HbA1c levels, the mean of HbA1c levels in both groups were still in normal range.

3.2. Comparison of NAFLD between FDR group and Non-FDR group

Based on US examination, proportion of NAFLD was found to be 26 cases (22,03%) with similar proportion for each group. Table 2 showed comparison of NAFLD prevalence in both groups. Table 3

Table 1
Baseline characteristics of FDR ofT2DM and non-FDR.

Characteristics	FDR of T2DM (n = 59)	Non-FDR (n = 59)	p value
Gender, n (%)			
Male	17(50.0)	17(50.0)	
Female	42(50.0)	42(50.0)	
Age (years), average (SD)	29.97(9.24)	29.08(5.55)	0.531
BMI (kg/m^2), average (SD)	22.91(3.20)	22.59(3.60)	0.614
ALT (U/L), median (min-max)	16.00(6–85)	17.00(8–103)	0.335
AST (U/L), median (min-max)	18.00(9–35)	17(13–71)	0.652
Triglyceride (mg/dL), median (min-max)	75.00(30–221)	76.00(38–185)	0.765
Normal triglyceride, n (%)	56 (94.9)	55 (99.4)	0.697
Abnormal triglyceride, n (%)	3 (5.1)	4 (6.8)	
HDL-C (mg/dL), median (min-max)	51.81(10.21)	50.73(11.24)	0.584
Normal HDL-C, n (%)	39 (66.1)	52 (88.1)	0.004*
Low HDL-C, n (%)	20 (33.9)	7 (11.9)	
LDL-C (mg/dL), average (SD)	127.93(34.18)	125.71(32.78)	0.719
Total cholesterol (mg/dL), average (SD)	186.64(35.23)	186.81(33.14)	0.772
HbA1c (%), average (SD)	5.01(0.39)	5.15(0.33)	0.027**
Fasting blood glucose (mg/dL), average (SD)	85.84(7.31)	85.10(8.15)	0.602
Waist circumference (cm), average (SD)	78.44(8.69)	78.00(9.76)	0.799
Normal waist circumference, n (%)	41 (69.5)	40 (67.8)	0.843
Abnormal waist circumference, n (%)	18 (30.5)	19 (32.2)	
Metabolic syndrome, n(%)			
Yes	11 (18,6)	3 (5,1)	0.023***
No	48 (46,2)	56 (94,9)	

SD: standard deviation; BMI: body mass index; ALT: alanine transaminase; AST: aspartate transaminase; HDL-C: high density lipoproteins cholesterol; LDL-C: low density lipoproteins cholesterol; FDR: first degree relatives; T2DM: type 2 Diabetes Mellitus.
*OR 3,81, CI95 = 1.47–9,91; **CI95 = 0,02–0,28; ***OR 4.28, CI95 = 1.13–16.23.

Table 2
Comparison of NAFLD between FDR group and Non-FDR group.

Variable	NAFLD	Normal	OR (CI 95%)	p
FDR of T2DM, n (%)	13 (22,03)	46 (77,97)	1 (0,507–1972)	1
non FDR, n (%)	13 (22,03)	46 (77,97)		

FDR: *First Degree Relatives*; T2DM: type 2 Diabetes Mellitus; OR: odds Ratio; CI: confidence interval.

Table 3
Characteristic of subjects with NAFLD in both groups.

Variable	FDR of T2DM	Non FDR
Obesity, n (%)[a]	5 (19,23)	5 (19,23)
Low HDL-C, n (%)[b]	4 (15,38)	1 (3,85)
Hypertriglyceridemia, n (%)[c]	2 (3,39)	2 (3,39)
Central obesity, n (%)[d]	9 (34,61)	10 (38,46)

FDR: First Degree Relatives; T2DM: type 2 Diabetes Mellitus; HDL-C: high density lipoproteins cholesterol; NAFLD: Non-Alcoholic Fatty Liver Disease.
[a] Body Mass Index ≥25.
[b] Serum HDL-C <40 mg/dL in men and <50 mg/dL in women.
[c] Serum triglyceride ≥150 mg/dL.
[d] Waist circumference ≥90 cm in men and ≥80 cm in women.

shows characteristic of subjects with NAFLD in both groups based on obesity, low HDL-C level, hypertriglyceridemia and central obesity. In subjects with NAFLD, the number of subjects with obesity, hypertriglyceridemia and central obesity were found similar in both groups. However, we found more subjects in FDR group had low HDL-C level compared to non-FDR group.

3.3. Analysis on covariates

Obesity, waist circumference, HDL-C and triglyceride level are components of metabolic syndrome which are known associated with NAFLD. From bivariate analysis (see Table 4), it was found that obesity, waist circumference, and triglyceride had statistically significant relationship ($p < 0.05$) with NAFLD.

Covariates with $p < 0.250$ in bivariate analysis were then included in the logistic regression analysis as seen in Table 5. In multivariate analysis it was found that central obesity and obesity had a statistically significant influence towards NAFLD.

Table 4
Bivariate analysis of covariates towards NAFLD.

Covariates	NAFLD		OR (CI 95%)	p value
	Yes	No		
Obesity[a]				
Yes, n (%)	16(51.6)	15(48.4)	8.213(3.131–21.547)	0.000*
No, n (%)	10(11.5)	77(88.5)		
Low HDL-C[b]				
Yes, n (%)	9(22.5)	31(77.5)	1.042(0.417–2.605)	0.930
No, n (%)	17(21.8)	61(78.2)		
Hypertriglyceridemia[c]				
Yes, n (%)	4(57.1)	3(42.9)	5.394(1.124–25.875)	0.021*
No, n (%)	22(19.8)	89(80.2)		
Central Obesity[d]				
Yes, n (%)	19(51.4)	18(48.6)	11.159(4.072–30.580)	0.000*
No, n (%)	7(8.6)	74(91.4)		

HDL-C: high density lipoproteins cholesterol; NAFLD: Non Alcoholic Fatty Liver Disease.
[a] Body Mass Index ≥25 kg/m^2.
[b] Serum HDL-C <40 mg/dL in men and <50 mg/dL in women.
[c] Serum triglyceride ≥150 mg/dL.
[d] Waist circumference ≥90 cm in men and ≥80 cm in women.

Table 5
Multivariate analysis of covariates towards NAFLD.

	Variable	OR (CI 95%)	p
Step 1	Central Obesity[a]	5292 (1736–16,130)	0,003
	Obesity[b]	5426 (1504–19,576)	0,010
	Hypertriglyceridemia[c]	1642 (0,291–9272)	0,574
Step 2	Central Obesity[a]	5395 (1778–16,373)	0,003*
	Obesity[b]	5781 (1639–20,399)	0,006*

[a] Waist circumference ≥90 cm in men and ≥80 cm in women.
[b] Body Mass Index ≥25 kg/m^2.
[c] Serum triglyceride ≥150 mg/dL.

4. Discussion

To the best of our knowledge, this is the first study conducted in Indonesia regarding NAFLD among young adult normoglycemic normotensive FDR of T2DM. Indonesia has the largest population in South East Asia which known as the second highest region of diabetic population according to International Diabetes Federation (IDF) [2]. The influence of ethnic variation in body fat distribution, age, and glucose tolerance status could give diversity of the result in this study although similar study had been done by Adibi et al. [18] in Iran. This study included non-FDR group which consist of people without family history of DM. We did age and sex matching between both groups to minimize the influence of age and gender on metabolic profile of study participants.

IR was found higher in FDR of T2DM than non-FDR in some studies. The previous study in Jakarta [20] reported that siblings of T2DM patients had high degree of IR determined by Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). A study by Kumar et al. in North India [21] reported significantly higher prevalence of IR in FDR of T2DM than that of non FDR (fasting plasma insulin/FPI 43.6% vs 11.24%; HOMA-IR 37.8% vs 12.47%). IR leads to hyperinsulinemia, impaired fasting glycemia, impaired glucose tolerance, and finally T2DM as confirmed by The Inter99 study done by Faerch et al. [22] Systemic hyperinsulinemia generates more lypolisis, rising of FFA, triglyceride level and visceral fat accumulation, which led to obesity and can cause NAFLD [22,23]. Higher level of IR in FDR of T2DM group is considered as a risk factor in the occurrence of NAFLD. Unfortunately, previous studies [14,18] did not stated clearly whether NAFLD in FDR of T2DM were dependent of IR rather than genetic vulnerability.

In this study we could not find the association of parent's history of T2DM with NAFLD. This finding is similar to study by Adibi et al. [18] which recruited 222 non-diabetic FDR of consecutive patients with T2DM aged 35–55 in Iran. They did not confirm significant association between NAFLD and FDR of T2DM, but stated that the relationship between the two variables seemed to be affected by other covariates, including BMI (overweight and obese) [18]. Previous studies [12,24] stated that NAFLD was significantly associated with several conditions, which were correlated with IR in particular obesity. In this study, the percentage of overweight and obese subjects in FDR group were higher than non-FDR group (45.7 vs 39%). This result was similar with study by Cederberg et al. [25] which demonstrated that individuals with FDR of T2DM tended to present with overweight/obesity, particularly abdominal obesity. In this study we found that central obesity and BMI $\geq$25 kg/m^2 were associated with NAFLD. Higher prevalence of overweight and obesity in subject with FDR of T2DM could increase the risk of this group to have NAFLD.

The previous research [18] also could not describe the association between FDR of T2DM and NAFLD because they included subjects with wide age range and prediabetes. Age, sex and insulin resistance were proven to have a good correlation with the occurrence of NAFLD. In this study, we recruited young adults (19–39 years old) and excluded subjects with glucose intolerance (HbA1c > 5,7%) and severe obesity (BMI $\geq$ 30 kg/m2) to minimize the effect of IR on NAFLD. Although we had limited the subjects with severe obesity and the proportion of NAFLD in both groups were not different, we found that the total subjects with low HDL-C and metabolic syndrome were higher in FDR group than non-FDR group (33.9% vs 11.9%; 18.6% vs 5.1%). This finding supported by Siewert et al. [26] who found that metabolic syndrome was higher in young adult FDR of T2DM than non FDR. Ishikawa et al. [27] found that obesity, in particular abdominal obesity expressed as waist circumference, is a well-known contributor to the development of metabolic syndrome. Metabolic syndrome is known as main risk factor in the occurrence of NAFLD [28]. Thus, FDR of T2DM population is still vulnerable to have NAFLD although it still needs prospective studies to evaluate the onset and progressivity of NAFLD in this group.

Among several metabolic abnormalities found in FDR of T2DM, our and previous studies revealed various result regarding the influence of family history of diabetes on metabolic and vascular disorders. Studies about endothelial dysfunction in FDR of T2DM consistently reported the role of family history of diabetes on the carotid intima medial thickness independent of IR [7,29,30]. Meanwhile, Adibi et al. [18] and our study concluded that the occurrence of NAFLD in FDR of T2DM is IR dependent.

Our research has several limitations. The number of subjects is small and the control group in this study mostly recruited from the employees of RSCM and may not represent the real common population. On the other hand, we didn't evaluate the influence of diets and physical activity, where these factors might influence in the occurrence of NAFLD.

5. Conclusion

The occurrence of NAFLD in FDR of T2DM was influenced by IR (central obesity and obesity). Although the proportion of NAFLD were similar in both groups, the proportion of metabolic syndrome was higher in FDR of T2DM groups than that of non-FDR, thus FDR of T2DM possess higher risk of NAFLD. Prospective studies are needed to determine the role of family history of T2DM in the onset and progression of NAFLD.

Conflicts of interest

None of the authors have any conflict of interest to declare.

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