

Correlation Between Lipid Profiles with Pancreatic β -Cell Function in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is characterized by 2 times higher blood glucose and lipid profile than non-diabetic people. Several studies indicated that pancreatic β cell dysfunction due to dyslipidemia is an independent risk factor T2DM. Dyslipidemia on T2DM can lead pancreatic β cell dysfunction. Objective: This study aimed to determine the correlation between lipid profiles (triglyceride, total cholesterol, LDL, and HDL) with pancreatic β cell function (HOMA- β) in patients with T2DM. Methods: This research method is a cross-sectional study of 50 patients with T2DM at Community Health Center (45-65 years old). Lipid profiles level were analyzed by glycerol-3-phosphate-oxidase (GPO) PAP method (Genius) and insulin level was analyzed by using ELISA. β cell function is measured using HOMA- β . Pearson Correlation test was used to assess the correlation between lipid profiles with HOMA- β (p value <0.05) Results: This study showed no significant relationship between triglyceride and HOMA- β (p= 0,430), total cholesterol with HOMA- β (p=0,717), LDL with HOMA- β (p=0,633), HDL with HOMA- β (p=0,754). There is no significant relationship between lipid profiles (triglyceride, total cholesterol, LDL, and HDL) and β cell function. For further research, it is recommended to examine other factors such as food intake by taking into account the drugs consumed.

Keywords: HOMA- β , lipid profiles, type 2 diabetes

1. INTRODUCTION

The prevalence of Diabetes Mellitus (DM) increase in Indonesia and in world. International Diabetes Federation (IDF) showed that 415 million people were diagnosed with DM and it will increase to 642 million (55%) in the 2040. Indonesia ranked 7 most diabetic population in the world (around 10 million). The national prevalence diabetic people in Indonesia were 6.8% [1]. All of DM patients in Indonesia, 80-90 % are Type 2 Diabetes Mellitus (T2DM). T2DM is a metabolic syndrome characterized by high blood glucose caused by insufficient insulin secretion, insulin resistance, or both. It is also followed by high lipid profile [2][3][4].

Lipid abnormalities are common in people with T2DM. Type 2 diabetes mellitus are usually characterized by high total cholesterol (T-Chol), high triglycerides (Tg), low high density lipoprotein cholesterol (HDL-C) and possibly by increased levels of small dense LDL particles. Low density lipoprotein cholesterol (LDL-C) levels may be moderately increased or normal [5]. Study in 2016 found that 74.11%

of T2DM patients had hyperlipidemia and 25.89% had normal (of 200 T2DM patients). The pattern of lipid abnormalities observed was high triglyceride in 46 (31.08%) patients, high LDL in 25 (16.89%), low HDL in 14 (9.45%), high cholesterol in 24 (16.21%) and combined hyperlipidemia in 39 (26.35%) diabetic patients [6]. Among of various factorsthat play a role, dislipidemia plays an important role in the pathogenesis of pancreatic β cell dysfunction [4].

Cholesterol homeostasis is fundamental in terms in process insulin secretion in pancreas β cells. Insulin granules are the major sites of intracellular cholesterol accumulation in β cells. Excess cholesterol changes insulin granule properties and alters the distribution of insulin granule membrane proteins leading defect for insulin granule exocytosis. Excess cholesterol also caused reduced glucose-stimulated insulin secretion from β cells. Excess cholesterol inhibits granule membrane remodeling, it is unlikely that such a defect in granule maturation fully accounts for the broad effect of cholesterol addition on a large portion of the granule population. The increased granule size results

primarily from direct alterations of the granule membrane induced by cholesterol addition. High cholesterol levels will cause an enlargement of insulin granules up to 80%. In addition, excess cholesterol will also cause interference or damage to the maturation process of insulin granules [7]. In addition, accumulation of excessive cholesterol in β cell pancreas is leading lipotoxicity which reduces insulin secretion, causing β cell dysfunction and reduce β cells pancreas mass [8]. Some studies determined that diabetes or prediabetes individuals have higher total cholesterol values than healthy individuals with normal glucose tolerance [9].

Beside cholesterol, high levels of triglyceride was found associated with pancreatic β cells damage. Hypertriglyceridemia resulted in significant triglyceride stores in the islets, which subsequently inhibited glucose-induced insulin secretion, at least in part, via reduced glucokinase activity in the islets [10]. High triglyceride (TG) were independent risk factors of β cell dysfunction in newly diagnosed T2DM [11].

Recent study have examined that there is relationships between hyperlipidemia and β cell function in patients newly diagnosed diabetes with hyperlipidemia and without hyperlipidemia [11]. Increasing total cholesterol and LDL-C cause β cell function worse. Some studies show that higher LDL-C is high and lower HDL-C as an independent risk factor for β cell dysfunction. also reported that high LDL values induced β cell apoptosis. Meanwhile, high HDL stimulates insulin secretion as well inhibits β cell apoptosis [8],[9],[12]. Low level of HDL-c is associated with an improved β -cell function in Chinese patients with newly diagnosed [13].

Although several studies have documented the effects dyslipidemia against β cell function in the subject hyperglycemia, β and cell function relationships dyslipidemia needs to be clarified. Some studies also reported that high LDL values induce β cell apoptosis [9], [14]. While HDL stimulates insulin secretion as well inhibits β cell apoptosis but cell β function decreases with increasing LDL value. This findings are accordance with study that reported that β cell function decreases in individuals with high LDL [9]. This study shows that LDL inhibits insulin secretion that is stimulated glucose and β cell proliferation. Pancreatic β cell function has a relationship significant negative with total cholesterol and LDL. There is no significant relationship between the function of β cells of the pancreas with HDL and triglycerides [15].

In rural Bangladeshi population, the prevalences of dyslipidemia, especially low HDL-C and high Tg were found to be alarmingly high. The proportion of subjects with unfavorable lipid profiles increased with degree of glucose intolerance. High levels of Tg in combination with low levels of HDL-C showed the strongest association with T2DM and prediabetes [5].

Pancreatic β cell dysfunction and resistance peripheral insulin are characteristics of T2DM markers. Interference with β cell function leads to which decrease in insulin secretion response to glucose is marker for diabetes. Type 2 diabetes mellitus (T2DM) is characterized by decreased

beta-cell function on the background of increased insulin resistance [16].

2. METHOD

Subject

The study design used cross sectional research with the participants of 50 outpatients with T2DM. All subjects were outpatients with T2DM in Yogyakarta Indonesia based on their inclusion criteria such as T2DM outpatients (fasting blood glucose between 80-350 mg/dL), agreed and signed the informed consent, able to communicate, no kidney or cardiovascular disease complication, 35-65 years old. Sampling was determined by convenience random sampling technique. After recruitment, data collected included age, sex, marital status, religion, ethnicity, number of families, diet taken, supplement consumption, herbal or tea consumption, history of illness in the last 1-3 months, family history, type and dose of drugs consumed, smoking status, presence of infection and presence abscesses as well as long-standing DM. These data are collected by interviews with patients conducted using questionnaires.

Study design

The design of this study uses a cross-sectional study that to find correlation between lipid profiles with HOMA- β .

Measurement of nutritional status

Nutritional status is measured using body mass index (BMI). Nutritional status is determined by anthropometric measurements including measurements of body weight (kg) and height (cm) in units of kg/m² by using the formula = weight (kg)

$$\text{Height squared (m}^2\text{)}$$

Weight was measured with minimum clothing using digital balance (Camry brand) 200 kg capacity with 0.1 kg sensitivity. Height was measured by microtoice with a length of 200 cm with 0.1 cm sensitivity without shoes in an erect standing position

Blood pressure measurement

Blood pressure values are average for three times of the systolic and diastolic blood pressure measurements. Blood pressure values are measured using a stethoscope and mercury sphygmomanometer (Omron brand).

Preparation of blood samples

Blood samples are used to obtain serum for examination of lipid profile levels, fasting blood glucose levels and fasting insulin levels. Before blood is drawn, patients are asked to fast for 8-10 hours to subsequently be taken blood samples. Fasting is a condition of no calorie intake but drinking water is permitted. Blood is drawn through the cubital veins which

is as much as 3 mL by using 3 mL syringe after disinfection was done at the collection site. Each venous blood sample taken was collected in a tube and then centrifuged at a rate of $2-3 \times 10^3$ rpm for 15 minutes to obtain serum. The serum is pipetted using a micropipette and put in an ependoff tube and labeled according to the randomization number and then stored in the refrigerator at -40°C to -80°C until an examination is carried out for checking lipid profile levels, fasting blood glucose levels and fasting insulin levels. Blood samples are taken by laboratory staff.

Examination of lipid profiles, fasting blood glucose and fasting insulin levels

Serum samples of all patients were analyzed for lipid profile, fasting serum glucose and fasting insulin levels. Lipid profiles such as total cholesterol and HDL (High Density Lipoprotein) cholesterol blood levels were measured using the cholesterol oxidase-p-amino phenazone method (CHOD-PAP method). Triglyceride levels were measured using glycerol-3-phosphate-oxidase (GPO) PAP method. Total cholesterol, HDL cholesterol and triglycerides were analyzed by the Diasys kit (Diasys diagnostic system GmbH Alte Strasse 9 65558 Holzheim Germany). LDL levels are calculated indirectly from total cholesterol concentration (ChC), HDL cholesterol concentration (HDL) and triglyceride concentration (TgC) were measured by using the formula of $\text{LDL} = \text{Total ChC} - (\text{TgC}/5 + \text{HDL})$ in mg/dL units. Fasting blood glucose levels are measured using the glucose oxidase-para amino phenazone (GOD-PAP) method. The principle of measurement is the enzymatic process of glucose oxidation by the glucose oxidase enzyme producing glucuronic acid & H_2O_2 , measured using the glucose oxidase-para amino phenazone (GOD-PAP) method in mg/dL units by the Diasys kit (Diasys diagnostic system GmbH Alte Strasse 9 65558 Holzheim Germany). Insulin levels were measured using Microparticle Immunoassay (ELISA method) with IU/ mL units. Fasting insulin levels were analyzed by the insulin ELISA kit (The Calbiotech A life science company).

Measurement of pancreatic β cell function

Pancreatic β cell damage was determined using HOMA- β index by measuring fasting glucose levels (mg/dL) and fasting insulin levels ($\mu\text{IU/mL}$). Pancreatic β cell function status was assessed using homeostasis beta assessment model for knowing the level of beta cell function (b%) by the formula: $(360 \times \text{fasting blood glucose (mg/dL)}) / (\text{fasting blood insulin (}\mu\text{IU/mL)} - 63)$ manually.

Statistical Analysis

All data were analyzed using software of SPSS 20.0 programme. The result of descriptive variables including antropometric data (weight, height), systolic blood pressure, diastolic blood pressure, blood lipid profiles markers level, fasting glucose marker level, and fasting insulin level were

presented as mean \pm standard deviation (SD). Normality data distribution is tested by One-Sample

Kolmogorov-Smirnov Test. Correlation between lipid profiles and HOMA- β are measured using Pearson Correlation Test. P-value less than 0.05 was considered statistically significant.

Ethical considerations

The study protocol was explained in detail to all participants. All intervention were executed after the respondents agreed and signed the informed consent. The study protocol was approved by Ethics Committee at Faculty of Medical Science Public Health and Nursing Gajah Mada University (Ethical clearance number KE/FK/00995/2018). At in the beginning of the study after explaining all steps of the study for patients a written consent was obtained from all participants and they were assured that their information will be kept totally secret. All of them were free to leave the study whenever they want. Respondents agreed and signed the informed consent. The most of the samples were characterized by married, Muslim, Javanese ethnicity and had more than ≥ 2 family members. All of them, 100% consumed lowering glucose drug with additionally blood pressure medication (44%) and hyperlipidemia drugs. Most of the samples were non-smokers and had long-standing diabetes (more than 1 year). We don't found any abscess and only 4 % of sample had an infection. Table 2 gives description of clinical characteristic and laboratory examination of samples.

3. RESULTS AND DISCUSSION

Participants in this study are 50 outpatients T2DM and most of them are female (74%). The average age of the samples is 55.64 years old. Table 1 shows characteristic subject in this research for detail.

Table 1. Characteristic Subject

Variables	N=50	%
Sex		
a. Female	37	74
b. Male	13	26
Marital status		
a. Married	45	90
b. Widower	5	10
Religion		
a. Islam	43	86
b. Catholic	5	10
c. Christian	2	4

Ethnic		
a. Java	48	96
b. Madura	2	4
Family number		
a. <2	2	4
b. ≥ 2	48	96
Medicine consumed		
a. Diabetes	40	80
b. Diabetes +hypertension	7	14
c. Diabetes+hiperlipid	3	6
Supplement consumption		
a. No consume	41	82
b. Consume	9	18
Herbal / tea consumption		
a. No consume	47	94
b. Consume	3	6
History of illness in the last 1-3 months		
a. No illness	38	76
b. Illness	12	24
Lowering glucose medication		
a. No consume	0	0
b. Consume	50	100
Blood pressure medication		
a. No consume	28	46
b. Consume	22	44
Smoking status		
a. Smoker	1	2
b. No smoker	49	98
Presence of infection	2	4
Presence of abscess	0	0
Duration of diabetes		
a. Newly (≤ 1 year)	5	10
b. Long (> 1 year)	45	90

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hyperlipidemia drugs. Most of the samples were non-smokers and had long-standing diabetes (more than 1 year). We don't found any abscess and only 4 % of sample had an infection. Table 2 gives description of clinical characteristic and laboratory examination of samples.

Table 2. Clinical Characteristic and Laboratory Test

Variable	Min	Max	Mean \pm SD	p-value*)
Age (year)	41	64	55.64 \pm 5.54	0.501
Weight (kg)	45.20	110.80	64.15 \pm 12.07	0.415
Height (cm)	136.10	167.60	153.55 \pm 6.91	0.932
Body mass index (kg/m ²)	19.78	39.44	27.12 \pm 4.13	0.796
Systolic blood pressure (mmHg)	103.00	188.00	145.10 \pm 20.21	0.984
Diastolic blood pressure (mmHg)	66.00	100.00	80.08 \pm 8.93	0.350
Fasting blood glucose (mg/dL)	88.00	304.00	148.66 \pm 46.70	0.591
Fasting blood insulin (μ U/dL)	1.07	60.45	12.27 \pm 10.58	0.027
Beta cell function (HOMA- β) %	4.95	255.80	67.35 \pm 5.57	0.172
Triglyceride (mg/dL)	63.00	621.00	212.94 \pm 129.45	0.071
Total cholesterol (mg/dL)	117.00	313.00	206.62 \pm 45.04	0.465
Low density lipoprotein (mg/dL)	35.00	198.00	117.45 \pm 34.15	0.426
High density lipoprotein (mg/dL)	29.00	101.00	47.58 \pm 12.04	0.602

*) One sample Kolmogorov-Smirnov Test

The ability of pancreatic beta cells to produce insulin is shown by the value of HOMA- β which is found in most of the HOMA- β values in low category. This shows that pancreatic beta cells in most T2DM patients have been damaged. Although statistically it does not show a significant relationship between lipid profiles with HOMA- β ($p \geq 0.05$) as shown in Table 3.

Table 3. Correlation Lipid Profiles With HOMA- β

	p-value*)
Triglyceride (mg/dL)	0,430
Total cholesterol (mg/dL)	0,717
Low density lipoprotein (mg/dL)	0,633
High density lipoprotein (mg/dL)	0,754

*) Pearson Correlation Test

The distribution of HOMA- β values based on lipid profiles are illustrated in table below. Low HOMA- β values are found in DMT2 patients with normal TG, LDL-c, and HDL-C levels also above normal cholesterol levels (moderate and high levels).

Table 4. Distribution of HOMA- β based On Triglycerides Level

Triglyceride	HOMA- β					
	Normal		Low		Total	
	n	%	n	%	n	%
Normal	4	25	12	75	16	100
Above normal	13	38.2	21	61.8	34	100

Diabetes mellitus type 2 patients with normal and not normal (moderate and high) TG levels have low HOMA- β values but however, it is more common in T2DM patients with normal TG values.

Table 5. Distribution of HOMA- β Based on Total Cholesterol Level

Total cholesterol	HOMA- β					
	Normal		Low		Total	
	n	%	n	%	n	%
Normal	10	41.7	14	58.3	24	100
Above normal	7	36.8	19	73.2	26	100

Low HOMA- β values are often found in patients with T2DM with cholesterol levels above normal (moderate and high).

Table 6. Distribution of HOMA- β Based on LDL-C Level

Low density lipoprotein	HOMA- β					
	Normal		Low		Total	
	n	%	n	%	n	%
Normal	4	30,8	9	69,2	13	100
Above normal	13	35,1	24	64,9	37	100

DMT2 patients with normal LDL levels had 69,2 % low HOMA- β values. Likewise, distribution of a low HOMA- β values were found in DMT2 patients with HOMA- β values is above normal (moderate and high LDL) too.

Table 7. Distribution of HOMA- β Based on HDL-C Level

High density lipoprotein	HOMA- β					
	Normal		Low		Total	
	n	%	n	%	n	%
Normal	7	30.5	16	69,5	23	100
Above normal	10	37	17	63	27	100

The distribution of low HOMA- β were also commonly found in DMT2 patients with normal HDL levels. It is well established that cholesterol homeostasis is fundamental for appropriate insulin secretory function of β cells [17], as excessive cholesterol accumulation in β cells may cause lipotoxicity and reduce insulin secretion, causing β cell dysfunction and decreased β cell mass. This study shows

that there is no significant relationship between lipid profiles and HOMA- β ($p \geq 0.05$) but we found a tendency that low HOMA- β values are often found in patients with T2DM with cholesterol levels above normal (moderate and high). This study also found that the number of samples with low HOMA- β values was greater than normal HOMA- β . This might be due to the fact that some of the samples were old (average age 55.64 years old). This is in line with research conducted by Fumiaki et al. (2013) that describe 1 in 4 cases of DM in older adults can be preceded primarily by β -cell dysfunction and that their risk can be missed by relying on conventional risk factors such as adiposity and atherogenic dyslipidemia. Among older adults, impaired β cell function is more common than younger adults [18]. This is in accordance with research conducted in China (2016) whereas in a Chinese population with different levels of glucose tolerance, TG/HDL-C and TG could be the predictors of insulin resistance (IR). The lipid ratios could not be reliable makers of β cell function in the population [19]. Another studies that are not in line with this research show that TG and HDL-C correlate with insulin resistance. Triglyceride and total cholesterol correlates negatively with β -response cells to insulin resistance in non-diabetic individuals [20]. Dyslipidemia is challenging with pancreatic β dysfunction cells in subjects with NGT and this is especially seen in people with elevated TC and LDL-C levels, especially men [9].

Beta-cell function and insulin sensitivity were significantly improved through a low-fat plant-based diet in overweight adults [21]. Dietary glycemic load, glycemic index, and refined grains intakes are associated with reduced β -cell function, and the quality of dietary carbohydrates may be relevant for maintaining β -cell function among individuals [22]. Besides food intake factor, consumption of anti-hyperlipidemia drugs is very influential on beta cell damage. Metformin and Acarbose can improvement of pancreatic β -cell function and insulin resistance in Chinese patients with newly diagnosed T2DM [13]. Recent research that conducted between June and September 2007, was designed to provide reliable data on the relationship between β cell function and lipid profiles in Chinese individuals without prior history of diabetes or prediabetes. Dyslipidemia is associated with dysfunction of pancreatic β cells in subjects with NGT and this is particularly evident in people with elevated TC and LDL-C levels, especially males [9].

4. CONCLUSION

There is no significant relationship between lipid profiles (triglyceride, total cholesterol, LDL, and HDL) with β cell function (HOMA- β). For further research, it is recommended to examine other factors such as food intake by taking into account the drugs consumed

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