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The Correlation Between the Event of Dyslipidemia and Proteinuria in Type 2 Diabetes Mellitus in Inpatients Installation in Medical Section of RSUD Dr. Soetomo Period January 2019 – January 2020

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***Abstract*: Lipid profile abnormalities are often found in people with diabetes mellitus. Diabetes mellitus patients, especially type 2, have hyperglycemia levels that are related to insulin resistance to facilitate hyperlipidemia which has an important role in the formation of atherosclerosis which causes narrowing of the blood vessel lumen and decreases blood flow velocity which causes reduced blood supply to the kidneys. In addition, hyperglycemic conditions can increase the permeability of blood vessels in the kidneys causing proteinuria through increased activation of protein kinase c enzymes and production of vasoactive hormone angiotensin II. Dyslipidemia caused by hyperglycemic conditions activates reactive oxygen species (ROS) that have an important role in podocyte apoptosis, increasing macrophage infiltration and excessive extracellular matrix production in glomeruli in diabetic conditions, contributing to the development of chronic kidney disease (CKD). One of the complications of diabetes mellitus is diabetic nephropathy which is indicated by proteinuria. The aim of the study is to determine the relationship between lipid profile and the occurrence of proteinuria in patients with type 2 diabetes. This research used retrospection with a cross sectional approach. The subjects in this study amounted to 61 patients with type 2 diabetes mellitus with dyslipidemia in RSUD Dr. Soetomo in January 2019-January 2020 with medical record. Dependent variable were lipid profile and proteinuria. The results of spearman tests showed that there was a significant relationship between HDL dyslipidemia with proteinuria levels in patients with type 2 diabetes mellitus (p=0.043, rs=0,260). There is a significant relationship between HDL dsylipidemia with proteinuria levels in patients with type 2 diabetes mellitus.**

***Keywords*: Diabetes Mellitus 2, Dyslipidemia, Nephropathy, Proteinuria.**

1. Introduction

According to the American Diabetes Association (2014), diabetes mellitus (DM) is a group of metabolic diseases characterized by an imbalance in insulin requirements and levels due to defects in insulin secretion, insulin action, or both to regulate blood sugar so that the hemoglobin level bound to sugar (Hb1Ac) is above normal value. Type 1 and type 2 diabetes are some types of diabetes mellitus [1], [2]. According to the International Diabetes Foundation (2019), Indonesia ranks eighth in the world in the prevalence of diabetes and it is estimated that by 2045 there will be 16.6 million people with DM [3].

According to WHO (2019), type 2 diabetes is the most common type of diabetes (90%) and is caused by varying degrees of beta cell defects and insulin resistance and is commonly identified with overweight and obesity [4]. According to Basic Health Research in Indonesia (Riskedas) (2018), the proportion of DM in Indonesia was 10.9% of the entire population of Indonesia [5]. According to WHO (2016) DM in Indonesia is more common in women (7.3%) than men (6.6%) [6].

One of the complications that is the main cause of death in diabetes mellitus patients is kidney disease. Chronic kidney disease caused by DM can progress to end-stage kidney disease [7]. On the other hand, approximately 43.2% of patients with diabetes and hypertension who do not have complications of chronic kidney disease still show indications of albuminuria [8].

Dyslipidemia is often found in people with diabetes mellitus. Most DM patients, especially type 2 have a degree of hyperglycemia that is related to insulin resistance to facilitate hyperlipidemia (especially cholesterol and triglyceride hyperlipidemia) [9]. Hyperglycemia can also increase the activation of the protein kinase c (PKC) enzyme which increases the production of vasoactive hormones such as angiotensin II (AT II), which in turn increases renal vascular permeability and causes proteinuria [10]. This condition is similar to hyperlipidemia that responsible for the formation of

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atherosclerosis thus cause narrowing of the blood vessels lumen and decreases the speed of blood flow which causes reduced blood supply to the kidneys [11].

In addition, dyslipidemia also causes the formation of reactive oxygen species (ROS), podocyte apoptosis, increases macrophage infiltration and excessive extracellular matrix production in the glomeruli in diabetic conditions, all of which contributes to the development of chronic kidney disease [10], [12], [13]. Furthermore, lipids can accumulate in the kidney and directly cause kidney injury by increasing lipid uptake via lipoprotein receptors/transporters, increasing lipogenesis, reducing efflux and consumption (oxidation), or through inflammation leading to podocyte damage in the glomerulus and extensive vascular endothelial damage resulting in proteinuria [13]-[15]. This can cause interference with the filtration process in the glomerulus and a decrease in kidney function [16]. Disruption of the filtration process can exacerbate complications in people with diabetes mellitus, namely diabetic nephropathy [17] accompanied by signs of proteinuria of 300 mg/day [14], [16], [18].

2. Aim of the Study

The aim of this paper is to know the correlation between the incidence of dyslipidemia and proteinuria in patients with type 2 diabetes mellitus.

3. Method

The study design used is cross-sectional by reviewing medical records of type-2 diabetes patients that had records of lipid profile and proteinuria in the inpatient installation of RSUD Dr Soetomo from January 2019 until January 2020. The inclusion criteria are Patients with type 2 diabetes mellitus who were hospitalized aged 18 years who had been diagnosed with proteinuria using the proteinuria scale and blood lipid levels between January 2019 – January 2020. Patients who received hemodialysis, who had hypertension, UTI, neoplasm, and congenital kidney disease are excluded. Patient's gender, age, value of lipids (Total cholesterol, triglyceride, LDL, and HDL), and presence and degree of proteinuria were collected from the patient's medical records. The data in this study were analyzed using non-parametric statistical methods using the SPSS 26 software by comparing variables in type 2 diabetes mellitus patients and presented in the form of a frequency distribution table.

4. Result and Findings

The final sample that met the inclusion and exclusion criteria was 61 patients.

1) Age

Based on the secondary data, the age mean of patients is 55.69 with ±8.64. The youngest and oldest patients were 36 years and 79 years old, respectively. Of the 61 samples, there were 4 patients (6.6%) at the age interval of 31-40 years, 12 patients (19.7%) at the age interval of 41-50 years, 26 patients (42.6%) at the age interval 51- 60 years, 16 patients (26.2%) were in the age interval of 61-70 years, and 3 patients (4.9%) were in the age interval of 71-80 years. So, it can be concluded that most of the samples are in the age interval of 51-60 years with a percentage of 42.6%.

2) Gender

A total of 28 patients (45.9%) were male while 31 patients (54.1%) were female.

3) Lipid Profile

Among the type-2 DM patients who also had proteinuria, 23 patients (37.7%) had total cholesterol dyslipidemia, 25 patients (41.0%) had triglyceride dyslipidemia, 19 patients (31.1%) had LDL dyslipidemia, and 38 patients (62.3%) had HDL dyslipidemia.

4) Relationship between the incidence of total cholesterol dyslipidemia and the occurrence of proteinuria

In type-2 DM patients with normal total cholesterol level, 6 (15.79%) had no proteinuria while 32 (84.21%) had proteinuria. Among type-2 DM patients who had total cholesterol dyslipidemia, 5 (21.74%) had no proteinuria while 18 (78.26%) had proteinuria. These findings were further analyzed using spearman correlation test. No significant correlation was found between total cholesterol dyslipidemia and presence of proteinuria in type 2 DM patients with a rs value of <0,10 [19] (rs=0.029) and p > 0.05 (P=0.822) [20].

Table 1
Frequency Distribution Table for the Relationship between Total Cholesterol Dyslipidemia and the Occurrence of Proteinuria

Variable	**Proteinuria**		**Total**	
	No	**Yes**		
Total Cholesterol Dyslipidemia	Sum (%)	Sum (%)	Sum (%)	
No	6 (15.79)	32 (84.21)	38 (100)	
Yes	5 (21.74)	18 (78.26)	23 (100)	
	Coefficient (rs)	**Sum (%)**	**T Statistic**	**P**
Total Cholesterol -Proteinuria	0.029	61 (100)	0.225	0.822

Table 2
Frequency Distribution Table for the Relationship between Triglyceride Dyslipidemia and the Occurrence of Proteinuria

Variable	**Proteinuria**		**Total**	
	No	**Yes**		
Triglyceride Dyslipidemia	Sum (%)	Sum (%)	Sum (%)	
No	6 (16.67)	30 (83.33)	36 (100)	
Yes	5 (20)	20 (80)	25 (100)	
	Coefficient (rs)	Sum (%)	T Statistic	P
Triglyceride -Proteinuria	0.018	61 (100)	0.142	0.888

Table 3
Frequency Distribution Table for the Relationship between LDL Dyslipidemia and the Occurrence of Proteinuria

Variable	Proteinuria		Total
	No	Yes	
LDL Dyslipidemia	Sum (%)	Sum (%)	Sum (%)
No	6 (14.29)	36 (85.71)	42 (100)
Yes	5 (26.32)	14 (73.68)	19 (100)
	Coefficient (rs)	**Sum (%)**	**T Statistic**	**P**
LDL -Proteinuria	0.058	61 (100)	0.450	0.654

Table 4
Frequency Distribution Table for the Relationship between HDL Dyslipidemia and the Occurrence of Proteinuria

Variable	Proteinuria		Total
	No	Yes	
HDL Dyslipidemia	Sum (%)	Sum (%)	Sum (%)
No	6 (14.29)	36 (85.71)	42 (100)
Yes	5 (26.32)	14 (73.68)	19 (100)
	Coefficient (rs)	**Sum (%)**	**T Statistic**	**P**
HDL -Proteinuria	0.058	61 (100)	0.450	0.654

5) Relationship between Triglyceride Dyslipidemia and the Occurrence of Proteinuria

In type-2 DM patients with normal triglyceride level, 6 (16.67%) had no proteinuria while 30 (83.33%) had proteinuria. Among type-2 DM patients who had triglyceride dyslipidemia, 5 (20%) had no proteinuria while 20 (80%) had proteinuria. These findings were further analyzed using spearman correlation test. No significant correlation was found between triglyceride dyslipidemia and presence of proteinuria in type 2 DM patients with a rs value of <0,10 (rs=0.018) [19] and p > 0.05 (P=0.888) [20].

6) Relationship between LDL Dyslipidemia and the Occurrence of Proteinuria

In type-2 DM patients with normal LDL level, 6 (14.29%) had no proteinuria while 17 (85.71%) had proteinuria. Among type-2 DM patients who had LDL dyslipidemia, 5 (26.32%) had no proteinuria while 14 (73.68%) had proteinuria. These findings were further analyzed using spearman correlation test. No significant correlation was found between LDL dyslipidemia and presence of proteinuria in type 2 DM patients with a rs value of <0,30 (rs=0.260) [19] and p > 0.05 (P=0.654) [20].

7) Relationship between HDL Dyslipidemia and the Occurrence of Proteinuria

In type-2 DM patients with normal HDL level, 6 (26.09%) had no proteinuria while 17 (73.91%) had proteinuria. Among type-2 DM patients who had HDL dyslipidemia, 5 (13.16%) had no proteinuria while 33 (86.84%) had proteinuria. These findings were further analyzed using spearman correlation test. A significant but weak and inverse correlation was found between HDL dyslipidemia and presence of proteinuria in type 2 DM patients with a rs value of <0,30 (rs=0.260) [19] and p < 0.05 (P=0.043) [20].

5. Discussion

The average age of the sample at the Doctor Soetomo Regional General Hospital is 56 years, with the youngest age being 36 years old and the oldest being 79 years old. Most patients were in the age range of 51-60, as many as 26 patients (42.6%). Research conducted by Wulandari (2012) found that diabetic nephropathy accompanied by dyslipidemia is more common in age group > 50 years with a percentage of 55.5% compared to those aged <50 years with a percentage of 44.5%. Likewise, a study by Miftahuljanna (2017) found that the highest incidence of dyslipidemia with diabetic nephropathy was in the 61-70year age group with a percentage of 39.6% [21]. This is because in old age the degree of vasodilation is higher due to endothelial changes marked by a decrease in glomerular filtration (eGFR) or higher proteinuria accompanied by dyslipidemia [22].

The results of gender frequency analysis in 61 samples of type 2 diabetes mellitus patients at Doctor Soetomo General Hospital showed that the incidence of proteinuria was not much different between men and women with the highest percentage located in men at 54.1%. This is in line with research conducted by Wulandari (2012) which found the highest frequency of dyslipidemia with diabetic nephropathy was in female patients with a percentage of 59.4% while in male patients it was only 40.6% and research conducted by Miftahuljanna (2017) obtained the highest frequency of dyslipidemia with diabetic nephropathy also in male patients with a percentage of 50.9% while in female patients 49.1%. This is in line with the theory of the androgen hormone in women, namely the hormone estrogen where the hormone is a protective regulation of diabetes mellitus and dyslipidemia, while men mostly have low testosterone so that men are more susceptible to diabetes mellitus than women. However, in women, an increase in lipid profiles such as triglycerides, LDL as a triggering factor for cardiovascular disease with a higher risk [23], [24].

Our research showed that 62.3% of type 2 DM had HDL dyslipidemia (low levels of HDL below normal), 62.3% of patients had normal total cholesterol levels, 59% of patients had hypertriglyceridemia, and 42 patients (68.9%) had normal LDL levels. This is in accordance with the results of research conducted by Wulandari (2012) in 89 cases of diabetes mellitus with diabetic nephropathy, where hypercholesterolemia was found in 51%, hypo-HDL in 56.8%, hyper-TG in 47.1%, and hyper-LDL in 40.6%. Meanwhile, Widiastuti (2003) studied 70

patients with Type 2 DM and found that hypercholesterolemia occurred in 70% of patients, hypertriglyceridemia was found in 44.29%, and a combination of the two was found in 40% [25]. In patients with diabetic nephropathy, lipid abnormalities were found, namely a decrease in HDL cholesterol levels and an increase in total cholesterol and triglyceride levels. Miftahuljanna (2017) also reported that there was a significant difference between dyslipidemic patients with NIDDM and proteinuria in LDL cholesterol levels and dyslipidemic patients with NIDDM and normoalbuminuria.

The results of this study indicate that there is a significant relationship with a weak correlation between HDL dyslipidemia and the occurrence of proteinuria in patients with type 2 diabetes mellitus (p=0.043). This is in accordance with Al-Jamiel's research (2014), where $p<0.005$ and $r=-0.24$ and the ratio of total cholesterol and HDL levels increases [26] according to the degree of proteinuria that causes atherogenesis [27]. This result is also in accordance with the study of Reverter (1994), where $p = 0.06$ and HDL levels will decrease significantly if proteinuria worsens [28]. Glomerular dysfunction that causes loss of small particles such as albumin and HDL is one of the causes of decreased HDL levels by looking at the inverse correlation for HDL-C [29]. It was found that patients with nephrotic syndrome were caused by a decrease in HDL levels but followed by severe proteinuria (2-4 with urine dipstick test) [30]. Acute renal failure is also often found in nephrotic syndrome which causes edema and proteinuria [31]. The results of this study are in line with the theory that in patients with type 2 diabetes mellitus it is often found that there is an increase in triglycerides, small LDL particles, and a decrease in HDL cholesterol that interacts with free radicals such as reactive oxygen species (ROS) and an increase in Apo B due to insulin resistance causes cell apoptosis. In the pancreas will cause atherosclerosis, renal vasodilation, and an increase in the glomerular filtration rate [32]. In addition, the predominant composition of triglycerides in VLDL which is a small form of LDL that has been broken down in a simple form functions like LDL. These conditions will accelerate the progression of renal deterioration, both glomerular or which will cause an indication such as proteinuria, which can occur with NIDDM or not [33], [34].

Our study showed no significant relationship between total cholesterol levels ($p = 0.822$), triglyceride levels ($p = 0.888$), and LDL cholesterol levels ($p = 0.654$) with the occurrence of diabetic nephropathy. This is not in accordance with Soni's (2005) research that showed one of the variables that affect the progression of diabetic nephropathy to terminal kidney failure is total cholesterol level ≥ 200 mg/dL ($p = 0.005$). This is also not in accordance with Wulandari's research (2012) that found triglyceride levels ≥ 150 mg/dL as a factor that affect the progression of diabetic nephropathy to terminal renal failure ($p = 0.016$). Our results also differ from Miftahuljanna's study (2017) that showed LDL level ≥ 130 mg/dL as a factor that affects the progression of diabetic nephropathy to terminal renal failure ($p = 0.045$).

Differences with previous studies may be due to different sampling criteria. This study uses a cross sectional method, with samples of type 2 diabetes mellitus patients with dyslipidemia followed by renal complications, either nephropathy or not, while the previous study used a cross sectional method with samples of patients with diabetic nephropathy with abnormal lipid levels (dyslipidemia) with lower baseline compared to this study [11], [21].

Albuminuria is a hallmark of diabetic nephropathy and plays a role in the prognosis of the condition. Diabetes Control Complications Trial (DCCT) states that albuminuria is associated with high levels of total cholesterol. Poor glycemic index is a major cause of dyslipidemia. In patients with poor glycemic control, the levels of TG-rich lipoproteins are higher. This increase is due to poor peripheral clearance resulting from lower expression of the ApoB100 receptor on the endothelial cell surface. In patients with uncontrolled type 2 diabetes, receptor recycling is also slow. Glycated ApoB100 has a longer interaction with its receptor thereby prolonging the second half-life of the LDL VLDL molecule [35].

The correlation between lipid parameters and renal function parameters in a Japanese study implies that dyslipidemia is associated with renal insufficiency in this population. Therapeutic interventions such as the use of statins to reduce cholesterol levels have been shown to reduce the risk of adverse cardiovascular events among subjects with kidney disease. Research data also show that total cholesterol levels are associated with a higher risk of death in patients with chronic renal failure [36].

There are other factors such as nutritional status and inflammation that can affect the results in this study. Previous studies have shown that in dialysis patients, higher total cholesterol is associated with a higher risk of death in the absence of malnutrition and inflammation, but a lower risk of death in the presence of malnutrition and inflammation. Therefore, it is possible that factors such as malnutrition and inflammation may influence the patient's condition caused by lipid disorders [37].

6. Conclusion

There is a significant correlation between HDL dyslipidemia and the occurrence of proteinuria in patients with type 2 Diabetes Mellitus. No significant correlation was found between total cholesterol, triglyceride, and LDL dyslipidemia and the occurence of proteinuria in Type-2 DM patients. A larger-scale cohort or case control study is suggested to better study the correlation between blood lipid profile values and occurence of diabetic nephropathy in type 2 DM patients.

Conflict of Interest

All authors have no conflict of interest.

Ethics Consideration

0768/LOE/301.4.2/I/2022 is provided by Dr. Soetomo general hospital as referral number of letter of exemption or ethic consideration letter.

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The author declares that we have no relevant or material financial interests that relate to the research described in this article.

Author Contribution

All authors have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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