Relationship Between Estimated Glomerular Filtration Rate With Plasma Lipid Levels In Non-Dialysis Diabetic Kidney Disease Patients

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***ABSTRACT: Aims:** To assess the relationship between estimated glomerular filtration rate (eGFR) and plasma lipid levels in non-dialysis diabetic kidney disease (ND-DKD) subjects.*

***Materials and methods :** In this cross-sectional study, outpatients from June to September 2020 who had been diagnosed with ND-DKD at Wahidin Sudirohusodo Hospital and Universitas Hasanuddin Hospital were enrolled. Creatinine was examined to determine eGFR based on the chronic kidney disease epidemiology collaboration (CKD-EPI) formulation, lipid profile, and metabolic characteristics. For statistical analysis, Pearson correlation test and Chi-Square test were performed, significant if the p < 0.05.*
***Results :** Of the 103 study participants analyzed with a mean age of 54,7 ± 9,1 years, it was found that the mean showed dyslipidemia, with plasma lipid levels in mg/dl were 254.1; 45.9; 156.2; 191.8 for total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), triglyceride (TG), respectively, and the mean eGFR value was 61.6 min ml/1.73m². From the analysis of the relationship between eGFR*

and plasma lipid levels, it was found that only the HDLc level was significantly associated with eGFR, and this relationship was only influenced by female gender.

Conclusions : There was a significant positive correlation between eGFR and HDLc level in ND-DKD subject where the lower the eGFR, the lower HDLc level.

Keywords : Non-dialysis diabetic kidney disease. Estimated glomerular filtration rate. Lipid plasma levels. Type 2 diabetes mellitus.

1.   INTRODUCTION

Diabetic kidney disease (DKD) is not only the main cause of end-stage kidney disease (ESKD) but also plays a major role as a risk factor for the development of cardiovascular disease (CVD). Although ESKD is the best-known consequences of DKD, the majority of patients actually die from cardiovascular disease, and one of the main risk factors for CVD in both diabetes mellitus (DM) and chronic kidney disease (CKD) is dyslipidemia. [1][2]

Dyslipidemia due to diabetes is caused by a condition of insulin resistance (IR) with an increase in the free fatty acid flux that occurs in the liver which then promotes the typical triad of diabetic dyslipidemia, namely high plasma TG concentration, reduced HDLc, and increased concentration of small dense low- density lipoprotein (sdLDL) particles. [3] Meanwhile, in non-dialysis dependent CKD and in hemodialysis patients, dyslipidemia is generally characterized by high TG, low HDLc, and normal or slightly decreased TC and LDLc, which is different with patients who underwent peritoneal dialysis where the dyslipidemia was more atherogenic. [4]

Under the conditions of DKD, the presence of IR and impaired insulin action in lipoprotein metabolism are the main mechanism in changing the lipid profile of these patients, and finally, an increase in plasma TG and a decrease in the ratio of lipoprotein lipase to liver lipase causes an accelerated HDL breakdown so that the end result shows an increase in TG and a decrease in HDL. [5] So, the main aim of this study was to assess the relationship between eGFR and plasma lipid levels in ND-DKD subjects.

2. MATERIALS AND METHODS

a. Research design

An observational with a cross-sectional study was performed at the outpatient of Wahidin Sudirohusodo hospital and Universitas Hasanuddin hospital during June-September 2020.

b. Research subject

All ND-DKD subjects over 18 years old and willing to take part in research with the approval of involvement in the study by signing the informed consent were included in the study by consecutive sampling. Patients who taking lipid-lowering drugs, corticosteroids, angiotensin-converting enzyme-inhibitor (ACE-I) / angiotensin receptor blockers (ARB), estrogen, oral contraceptives, pregnant, suffering from nephrotic syndrome or hypothyroidism were excluded from the study. The subjects were diagnosed with DKD if the

kidney disease develops from DM characterized by albuminuria or decreased eGFR or both persistently at least two out of three examinations for at least three months, together with diabetic retinopathy and no signs of other forms of kidney disease. [(6)(7)] Non-dialysis DKD subjects in this study are type 2 diabetes mellitus (T2DM) patients who are accompanied by DKD and have not undergone dialysis at any eGFR.

c.   *Research data collection*

Age, gender, and personal medical history were recorded using an interviewer-administered questionnaire.

Body mass index (BMI) is an indicator to determine overweight (BMI 23.0 - 24.9) and obesity (BMI> 25), the calculation is body weight (kg) divided by height (m) and universally expressed in units of kg/m2. In this study, subjects with a BMI less than normal were included in the normal BMI group.

Hypertension was considered in participants with systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg and/or with the previous diagnosis of hypertension, and/or with antihypertensive medication.

Glycemic control based on HbA1c levels, uncontrolled if HbA1c $\geq$ 7%.

The eGFR is calculated based on the creatinine value using the CKD-EPI formulation, which is according to the Kidney Disease Improvement Global Outcomes (KDIGO) guidelines. This study was divided into only three eGFR groups, namely the eGFR $\geq$ 90 ml/min/1,73 m2, eGFR 60-89 ml/min/1,73 m2, eGFR <60 ml/min/1,73 m2.

Levels of each plasma lipid fraction are measured in mg/dl, with the following classification: high TC if $\geq$ 200, low HDLc if < 40 (male) and < 50 (female), high LDLc if $\geq$ 100, high TG if $\geq$ 150. All plasma lipid levels other than the undesirable levels are included as normal lipid levels.

Blood sampling only once for all required variables, after previously fasting for 8-10 hours.

d.   *Research data analysis*

The data were analyzed by using Statistical Package for the Social Sciences (SPSS) version 22 with descriptive statistical analysis, Chi-Square statistical test, and Pearson correlation test. The statistical test results were significant if the $p < 0.05$.

e.   *Ethical approval*

All procedures performed in this study involving human participants were in accordance with the ethical clearance approval from the Ethics Commission of Biomedical Research in Humans, Faculty of Medicine, Hasanuddin University, Makassar, number of 574/UN4.6.4.5.31/PP36/2020

3.   RESULTS

a.   Characteristics of the research subjects

Shows data analysis result among 103 subjects aged 36-79 years, with the mean age was 54,7 ± 9,1 years. The mean BMI value was 24,9±3,7 kg/m^2, while SBP and DBP were 142.5 ± 21.5 mmHg and 82.2 ± 12.9 mmHg, respectively. Of the 92 subjects who were tested for HbA1c, the average was 9.2±1,8 %. The lipid profile description were TC between 97-537 mg/dl with mean 254,1±66,8 mg/dl, HDLc between 20-84 mg/dl with mean 45,9±12,5 mg/dl, LDLc between 41-413 mg/dl with mean 156,2±54,3 mg/dl, and TG between 36-581 mg/dl with mean 191,8±101,2 mg/dl.

Table 1

TABLE 1				
CHARACTERISTICS OF RESEARCH SUBJECTS (N = 103)				
VARIABLES	MINIMUM	MAXIMUM	MEAN	SD
AGE (YEARS)	36	79	54,7	9,1
BMI (KG/M^2)	17,9	38,0	24,9	3,7
SBP (MMHG)	100	200	142,5	21,5
DBP (MMHG)	60	110	82,2	12,9
HBA1C (N = 92)(%)	5,6	15,0	9,2	1,8
TC (MG/DL)	97	537	254,1	66,8
HDLC (MG/DL)	20	84	45,9	12,5
LDLC (MG/DL)	41	413	156,2	54,3
TG (MG/DL)	36	581	191,8	101,2
EGFR (ML/MIN/1,73M^2)	5	115	61,6	28,6

3.2.Relationship between eGFR and plasma lipid level

Table 2 shows that there was a significant *(p = 0,010)* positive correlation between eGFR and HDLc level, and negative correlation that had not reached a significant level between eGFR and TC level *(p = 0,291)*, eGFR and LDLc level *(p = 0,471)*, eGFR and TG level *(p = 0,554.*

Analysis of the relationship between eGFR and the levels of each lipid fraction by Pearson correlation in Table 2, is illustrated in the scatter diagram below (Figure 1), where it is illustrated that there is a positive correlation with a correlation coefficient (R) = 0,252 between eGFR and HDLc level, where the lower the eGFR, the lower the HDLc level (A) which is statistically significant   (p < 0,05). The diagram also illustrated that there were a negative correlation, between eGFR and TC level (B) with R = -0,105; eGFR and LDLc level (C) with R = -0,072; eGFR and TG level (D) with   R = -0,059, where the lower the eGFR, there was a slight tendency to increase TC, LDLc and TG, but statistically had not reached a significant level (p > 0.05).

Table 2		
Relationship between egfr with plasma lipid levels according to pearson correlation		
Plasma lipid levels	Egfr value (n = 103)	
	R	P
Tc	-0,105	0,291
Hdlc	0,252	0,010
Ldlc	-0,072	0,471
Tg	-0,059	0,554

A. eGFR and HDLc correlation *(p=0,010)*   B. eGFR and TC correlation *(p=0,291)*

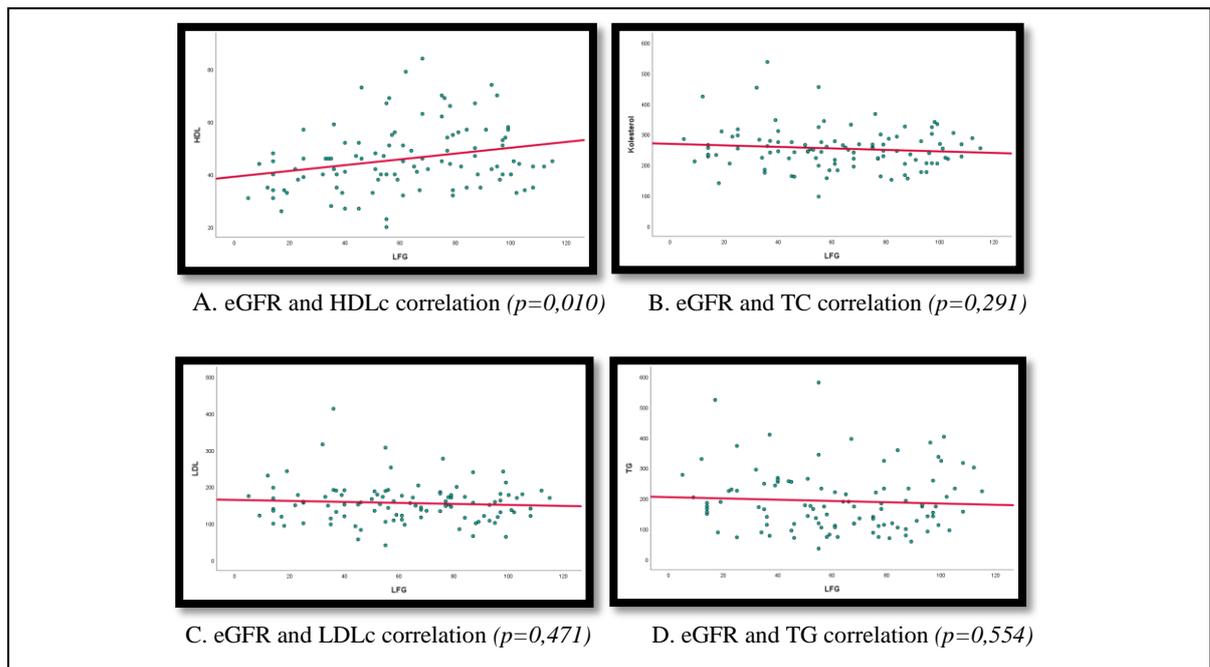C. eGFR and LDLc correlation *(p=0,471)*   D. eGFR and TG correlation *(p=0,554)*

Figure 1. Scatter diagram of the relationship between eGFR and HDLc, TC, LDLc, and TG

3.3. Factors influence the relationship between eGFR reduction and decrease of HDLc level

Table 3 shows that among the factors such as gender, age, BMI, blood pressure, and HbA1c that were assessed as having an effect on the association of decreased HDLc levels with a decrease in eGFR, only gender which was significant ($p < 0.05$) affect the relationship, where female subjects have low HDLc level as much 40 people (62.5%), and male gender only as much 12 people (30.8%). Meanwhile, other factors described having no significant ($p > 0,05$) effect on this relationship.

Table 3

Factors influence the relationship between decrese in egfr and decrease of hdlc level				
Factors influence	Total n=103 (100%)	Hdlc level		P
		Low	Normal	
Gender	Male,n=39(100%)	12 (30,8%)	27 (69,2%)	0,002
	Female,n=64(100%)	40 (62,5%)	24 (37,5%)	
Age (years)	≥60 years,n=31(100%)	13 (41,9%)	18 (58,1%)	0,255
	<60 years,n=72 (100%)	39 (54,2%)	33 (45,8%)	
Bmi (kg/m^2)	Normal weight,n=30(100%)	16 (53,3%)	14 (46,7%)	0,348
	Overweight,n=28(100%)	17 (60,7%)	11 (39,3%)	
	Obese,n=45(100%)	19(42,2%)	26 (57,8%)	
Hypertension (mmhg)	Yes,n=64(100%)	28 (43,8%)	36 (56,3%)	0,080
	No,n=39(100%)	24 (61,5%)	15 (38,5%)	
Hba1c (n=92) (%)	Uncontrolled,n=85(100%)	42 (49,4%)	43 (50,6%)	0,739
	Controlled,n=7(100%)	3 (42,9%)	4 (57,1%)	

4.   DISCUSSION

There were 103 subjects enrolled in this study with a mean age of 54.7 ± 9.1 years. In the study of Palazhy et al, the age of T2DM patients with overt nephropathy was between 54.28 ± 9.26.[8]

The majority of the subjects of this study were women compared to men. In accordance with the study of Onuigbo J, et al where the prevalence of women is higher (51.4%) than men (48.6%). [9] Margaret Yu, et al. stated that women with diabetes have a greater prevalence in developing DKD due to the risk factors like obesity, hypertension, and poorer glycemic control which more dominant in women. [10]

The mean BMI of this study was 24.9 ± 3.7. Similar to the study by Sanoop M, et al with an average BMI of 24.51 ± 4.97. [11] The average subjects of the study by Hill CJ et al were obese, which is showing a strong association with DKD.[12]

Blood pressure predominantly showed hypertension, as well as the study by Dash et al, with a prevalence of 78,7%. [13]

For glycemic control, the majority of the study subjects showed uncontrolled with average level of HbA1c of 9.2 ± 1.8, almost the same as the Kolhar and Priyanka study with a mean HbA1c level of 9.0 ± 2.1. [14]

Characteristics of lipid levels in this ND-DKD subject were 254.1 ± 66.8 of TC; 45.9 ± 12.5 of HDLc; 156.2 ± 54.3 of LDLc; and 191.8 ± 101.2 of TG. This was similar to the study of Palazhy S and Viswanathan V in diabetic nephropathy patients which lipid levels characteristics were 211.76 ± 70.27; 40.91 ± 11; 121.18 ± 45.27; and 189.64 ± 114.71 for TC, HDLc, LDLc, and TG, respectively.[8]

So all the characteristics of the metabolic factors of the subjects in our study are in accordance with various studies that show risk factors for developing CKD in diabetes patients are obesity, hypertension, poor glycemic control, and dyslipidemia.

The eGFR subject in this study averaged 61.6 ± 28.6. In contrast to the study by Russo et al in 15,362 DKD subjects with T2DM with an average eGFR of 87 ± 13. [15]

From the analysis of the relationship between eGFR and plasma lipid levels with Pearson correlation test, it was obtained that only the HDLc level had a positive correlation with eGFR   ($p <0.05$), where the lower the eGFR, the lower HDLc level. These results are in line with research by Yang X et al in a large prospective study which shows that a decrease in HDLc levels could predict a decrease in eGFR.[16] Studies by The Health Professionals Follow-Up Study (HPFS) and Atherosclerosis Risk in Communities Study show that hypertriglyceridemia and decreased HDLc levels are characteristics of dyslipidemia which associated with decreased in eGFR of individuals with T2DM.[17][18] Various studies have stated that in the condition of DKD, plasma lipid abnormalities especially in TG and HDLc.[8][19]

In this study, only HDL shows significant relationship with eGFR by a positive correlation, while TG showed no significant relationship although the TG correlation coefficient shows a negative value, which means that there is a negative relationship but it does not reach a significant level. The decrease in HDLc levels occurs due to a decrease in the levels of apolipoproteins AI and AII as the main components of HDL, disruption of the activity of the enzyme lecithin-cholesterol acyltransferase, which is important for esterification of free cholesterol in HDL and increased cholesterol ester transfer protein (CETP) activity, which supports the transfer of cholesterol esters from HDL to TG-rich lipoproteins.[8][19] Based on this study, it can confirm that a decreased HDLc level can predict a decrease eGFR in ND-DKD patients.

In further analysis of the factors that influence the relationship between decreased eGFR and low HDLc levels, it was found that only gender had a significant influence ($p < 0,05$) whereas lower HDLc levels were more common in women than in men. While age and metabolic factors such as BMI, blood pressure and HbA1c didn't affect this relationship ($p > 0.05$). This contradicts the study which states that age, hypertension, and BMI affect HDLc levels. [20]

HDLc levels vary with ethnicity and sex. In general, women have higher HDLc levels than men. However, this gender difference is less pronounced in Asia, including China and Japan, than in Europe and America. The study by HJ Kim et al showed that gender differences were significantly associated with HDLc levels where the percentage of low HDLc was higher in males than in females. Likewise several studies elsewhere, also show the same results where low HDL is more dominant in men. The sex difference in HDL levels is partly explained by estrogen, where estrogen is known to reduce macrophage metabolic activity by accumulating lipids, while testosterone is the opposite. However, the relationship between sex hormones and differences in HDL levels still needs to be investigated.

5. STUDY LIMITATION

The limitation of this study was no T2DM patients without complications of DKD as a control subject. This study also didn't check albumin levels, which is known that the

condition of albuminuria that occurs in DKD patients causes protein loss resulting in hypoalbuminemia which results in increased albumin synthesis in the liver accompanied by increased lipoprotein synthesis
.

6. CONCLUSION

There was a relationship between eGFR and plasma lipid levels in ND-DKD subjects, where a significant decrease in eGFR correlates positively with a decrease in HDLc level.

ABBREVIATIONS

BMI	body mass index
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease-epidemiology collaboration (CKD-EPI)
CVD	cardiovascular disease
DBP	diastolic blood pressure (DBP)
DKD	diabetic kidney disease
ESKD	end-stage kidney disease
HDLc	high-density lipoprotein cholesterol
LDLc	low-density lipoprotein cholesterol
ND-DKD	non-dialysis diabetic kidney disease
sdLDL	small dense Low-density lipoprotein
SBP	systolic blood pressure (SBP)
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TG	trigliceryde
VLDL	very low-density lipoprotein

CONFLICT OF INTEREST

No potential conflict of interest relevant to be declared

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