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Research Article

Dyslipidemia in Renal Dysfunction among Non-diabetic Individuals from the 2019 Indonesian Cohort Study: A Cross-Sectional Study

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ABSTRACT

The aim of this study was to investigate the relationship between dyslipidemia and the estimated Glomerular Filtration Rate (eGFR) values in a healthy population without a history of diabetes mellitus. Data were part of the cohort study database of 2019. Data analysis was perfomed using descriptive and inferential statistics with linear regression in 893 of 1,545 non-diabetic participants. The results showed that the average cholesterol levels, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), and triglycerides were 196.75, 48.71, 123.37, and 109.56 mg/dL, respectively, and the average eGFR level of the respondents was 98.47±15.50 mg/dL. This study found that age, HDL levels, and LDL levels had a significant relationship with eGFR ($p<0.05$). It was concluded that increasing age and LDL levels and decreasing HDL levels would decrease eGFR.

INTRODUCTION

The incidence of non-communicable diseases is increasing in developing countries; one of these diseases is Chronic Kidney Disease (CKD), often refrred to as chronic kidney failure. Based on data from the Basic Health Survey in Indonesia, which was identified using respondents' admissions and doctors' diagnoses of CKD, the incidence of this disease incidence has almost doubled, from 0.2% in 2013 to 0.38% in 2018 (MoH RI 2013; 2018).

Chronic kidney disease is a condition in which the kidneys have difficulty filtering blood due to kidney damage. Based on the level of kidney function, there are five stages that describe the condition of CKD. The staging of CKD is determined by estimating the Glomerular Filtrate Rate (eGFR), which is measured by how well the kidneys filter the blood. Kidney disease is divided into five main stages, ranging from stage 1 (mild) to stage 5 (kidney failure). The staging category is determined based on eGFR as follows: eGFR values greater than or equal to 90 mL/min/1.73 m^2 indicates stage 1 (mild kidney damage), eGFR of 60–89 mL/min/1.73 m^2 is an indication of stage 2 (slight loss of kidney function), while stages 3a & 3b (eGFR of 30–59 mL/min/1.73 m^2) are classified as mild to severe loss of kidney function, stage 4 is when the kidney is in a state of severe decompensation (eGFR of 15–29 mL/min/1.73 m^2), and stage 5 is a condition of renal failure or near renal failure (eGFR of less than 15 mL/min/1.73 m^2) (Chen *et al.* 2013; Theofilis *et al.* 2021).

Several methods of calculating eGFR have been studied. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation method is generally more accurate than the Modification of Diet in Renal Disease (MDRD) eGFR calculation method (Levey & Stevens 2010). The CKD-EPI calculation method is also more accurate than the MDRD method for assessing eGFR levels in healthy populations in Asia without a history of diabetes, hypertension, and kidney disorders (Teo *et al.* 2014).

The eGFR in chronic kidney disease can be influenced by various factors such as age, sex, serum creatinine level, diet, and several clinical parameters, such as blood glucose levels and lipid profiles (Arifa *et al.* 2017). Other clinical parameters such as dyslipidemia have also

been proven to affect the kidneys, especially in individuals with obesity or overweight and hyperglycemia, because it will burden the work of the renal organs (Kurniati & Tahono 2016; Navratilova *et al.* 2020). Significant increases in total cholesterol, triglyceride, and low-density lipoprotein levels are frequently associated with an increased likelihood of a decreased estimated Glomerular Filtration Rate (eGFR) and the development of chronic kidney disease (Liang *et al.* 2020). In the early stages of CKD, disturbances in lipoprotein metabolism are evident and usually progress toward reduced kidney function. Dyslipidemia has a major influence on the pathogenesis of CVD and impaired kidney function (Tsimihodimos *et al.* 2011).

Dyslipidemia in people with kidney failure is characterized by increased levels of total cholesterol, Triglycerides (TGs), and Low-Density Lipoprotein Cholesterol (LDL-C) and decreased levels of High-Density Lipoprotein Cholesterol (HDL-C) (Adejumo *et al.* 2016). In addition, a higher Body Mass Index (BMI) has been associated in large population-based studies with the development of a low estimated Glomerular Filtration Rate (GFR), the development of End-Stage Renal Disease (ESRD), which can occur in people at any age, and a more rapid loss of estimated GFR over time. In individuals with a history of CKD, an increase in BMI or obesity class II or higher is considered a risk factor for the rapid development of CKD itself (Kovesdy *et al.* 2017).

Studies based on several parameters, including clinical chemistry, have been widely conducted to predict chronic kidney disease as characterized by a decreased eGFR value, but these studies are still rarely conducted on healthy people, especially the population who are the respondents in cohort studies in Indonesia (Sulistiowati & Idaiani 2015). Therefore, this study was conducted to analyze the relationship between several clinical chemistry parameters in predicting the decline of eGFR in the study population of the Non-Communicable Disease Risk Factors Cohort in Indonesia.

METHODS

Design, location, and time

This study is a cross-sectional study using data collected during the Biomedical Cohort Study of Risk Factors for Non-communicable Diseases in 2019, which sampled from five districts in the city of Bogor, West Java Province. The data collection was conducted from March to December 2019 and was approved by the Ethics Committee of the Research and Development Agency No.LB.02.01/2/KE. 120/2019.

Sampling

Inclusion criteria for this study were members of the target population aged over 25 years who did not have diabetes mellitus or prediabetes and who had fasting and 2-hour postprandial glucose test results. Exclusion factors were members of the target population who had diabetes mellitus or prediabetes and did not have complete glucose test results as required by the inclusion criteria. Another exclusion criterion was the condition of the lysed blood serum samples. There were 894 out of 1,545 respondents who did not have diabetes mellitus or prediabetes.

Data collection

The respondents in this research were women and men aged 28 years and above. They were interviewed for their health data using a questionnaire, had their blood drawn for analysis, and underwent other medical examinations.

The respondents' blood samples were processed by centrifugation to obtain serum, which was then analyzed using a clinical chemistry tool branded Pentra® for blood analysis parameters such as total cholesterol, LDL, HDL, triglycerides and serum creatinine. The measurement of clinical parameters was performed according to the Standard Operational Procedure (SOP), which had undergone internal and external validation tests, and was performed with the assistance of a clinical pathologist.

In this study, fasting and 2-hour postprandial blood glucose levels in the normal category, which are 70–99 mg/dL and 70–139 mg/dL, respectively, are based on categorization by the Indonesian Association of Endocrinologists (PERKENI 2021).

Lipid profile categorization in this study follows the guidelines issued by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III). Normal cholesterol level is <200 mg/dL, normal LDL is <100 mg/dL, normal triglyceride is <150 mg/dL, and high level of HDL is ≥40 mg/dL for men and ≥50 mg/dL for women. Estimated glomerular filtration rate

(eGFR) was determined using the Collaborative Chronic Kidney Disease Epidemiology (CKD-EPI) eGFR calculation method with the aforementioned clinical chemistry tools. The normal level of creatinine is 0.7–1.2 mg/dL for men and 0.5–1.0 mg/dL for women (Levey AS *et al.* 2009). The calculation of eGFR followed the equation of the variables of sex, age, and serum creatinine levels. The equation formula for calculating eGFR according to the CKD-EPI method for men is 142 × (serum creatinine (mg/dL) /0.9)$^{-0.302}$ x 0.9938$^{\text{Age (years)}}$, while for women it is 142 × (serum creatinine (mg/dL) /0.7)$^{-0.241}$ x 0.9938$^{\text{Age (years)}}$ x 1.012.

Data analysis

Data analysis was carried out descriptively for characteristics and inferential. This study used multivariate analysis of variables using multiple regression analysis with age, sex, and lipid profile as independent variables and eGFR as the dependent variable. Data were processed using SPSS version 25.0 and analyzed using statistical regression tests. Statistical significance was set at $p<0.05$.

RESULTS AND DISCUSSION

Respondent characteristics and blood biomarkers

The characteristics of the respondents in this analysis included data on sex, age, blood lipid profile, creatinine level, and blood glucose. An estimated glomerular filtration rate is categorized according to categorical and numerical variables, as presented in Table 1. This study, which started 894 respondents, ended with 893 respondents because one respondent did not meet the inclusion criteria. The respondent was excluded from this study because of incomplete data from blood glucose tests (Fasting Plasma Glucose (FPG) test and Oral Glucose Tolerance Test (OGTT) or 2-hour postprandial glucose test).

The respondents in this study were people who did not have diabetes or prediabetes and were between the ages of 28 and 75 years (with a mean age of 47 years). The average cholesterol, HDL, LDL, and triglyceride levels were 196.73, 48.67, 123.49, and 107.00 mg/dL, respectively. The average creatinine level of the respondents was 0.77 mg/dL. Meanwhile, the average blood glucose levels of the respondents were 89.62 mg/dL (FPG) and 107.19 mg/dL (2-hour postprandial glucose) (Table 1).

The categorization of lipid profile, creatinine and blood glucose levels, and glomerular filtration rate of the respondents is described in Table 2. There were more than 50.0% of the respondents had normal total cholesterol and only 10.0% had a high level of cholesterol. High HDL levels were found in more than 50.0% of the respondents in this study. High LDL levels were found in 10.4% of the total respondents, but more than 30.0% of the respondents had LDL levels above normal limits. Less than 6.0% of the respondents had high triglyceride levels and more than 10.0% had triglyceride levels that exceeded normal levels. However, the majority of the respondents, more than 80.0%, had normal triglyceride levels.

The results of this research show that more than 50.0% of the non-diabetic respondents had relatively good lipid profiles, characterized by more than 50.0% of the respondents having normal cholesterol levels, high HDL levels, and normal triglyceride levels. Meanwhile, more than 50.0% of respondents had normal and near-normal levels of LDL. In addition, this study also found that less than 50.0% of a total of 893 non-diabetic respondents had dyslipidemia.

The eGFR values of the non-diabetic respondent in the abnormal category with the category of mild to severe loss and failure or close failure was 1.8 % of respondents and it can be concluded that the majority, more than 98.0% of all respondents have a normal eGFR. This study showed that, on average, the lipid profiles of the respondents were good, similarly, the eGFR of the respondents was also mostly normal.

This result of this study was similar to that of another study. A hospital-based case study concluded that dyslipidemia is common in non-diabetic patients with CKD. Dyslipidemia was found in three out of four patients with CKD, with high levels of LDL and low levels of HDL. Lipid parameters and disease development have a high degree of association statistically significant for cholesterol, triglyceride, and HDL levels (Lahane *et al.* 2022). Some studies have concluded that dyslipidemia is possibly a risk factor for kidney disease. Atherosclerosis risk associated with kidney disease in the Community Study found that an increased risk of developing kidney dysfunction was associated with low HDL cholesterol levels (Reiner *et al.* 2011). This

Table 1. Characteristics of respondents by sex, age, blood lipid profile, creatinine level, blood glucose, and estimated glomerular filtration rate

Variable	n=893	%	Mean±SD	Min.	Max.
Sex					
Male	276	30.9			
Female	617	69.1			
Age (years)					
Young adults (26–35 years)	93	10.4	32.90±1.99	28	35
Middle-age adults (36–55 years)	600	67.2	44.98±5.59	36	55
Old adults/Elderly (>55 years)	200	22.4	62.13±4.75	56	76
Parameters					
Cholesterol (mg/dL)			196.73±34.23	106.00	427.00
HDL (mg/dL)			48.67±10.85	22.00	99.00
LDL (mg/dL)			123.49±29.10	34.00	242.00
Triglyceride (mg/dL)			107.00±58.44	32.00	492.00
Creatinine (mg/dL)			0.77±0.18	0.40	1.70
FPG (mg/dL)			89.62±5.81	53.00	99.00
OGTT or 2-hours postprandial glucose (mg/dL)			107.19±17.98	55.00	139.00
eGFR			98.47±15.50	41.80	130.79

HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; FPG: Fasting Plasma Glucose; SD: Standard Deviation; OGTT: Oral Glucose Tolerance Test; eFGR: estimated Glomerular Filtration Rate; Min: Minimum; Max: Maximum

supports the relationship between the results of this study and other studies that a relatively good lipid profile is associated with a low risk of CKD, which was characterized by a relatively high eGFR in the respondents in this study. The finding that distinguished this study from several other studies was the relationship between increased triglycerides and decreased eGFR. This study concluded that there was no significant relationship between triglycerides and eGFR, whereas several studies concluded that high triglyceride levels were associated with eGFR.

The relationship between age, sex, and lipid profile and estimated glomerular filtration rate (eGFR) is shown in Table 3. It was shown that HDL, LDL, and age had a significant relationship with eGFR with p-values of 0.003, 0.028, and <0.001, respectively. Meanwhile, sex and total cholesterol did not have a significant relationship with eGFR in the results of this study. This study also found that triglyceride tended to have a significant relationship with eGFR (p=0.074). The F-test on the resulting multivariate regression showed a significant slope deviation from zero (p<0.05) and the fit was R2=0.413. Decreasing HDL levels, increasing LDL levels, and increasing age will decrease eGFR, which means that the risk of kidney dysfunction increases.

This finding is similar to that of other studies that have show a significant relationship between age and eGFR. This study concludes that young people have higher eGFR than older people (Yue *et al.* 2021). Another study showed that the prevalence of Chronic Kidney Disease (CKD), which is associated with decreased eGFR in the general population, increases with age, with a prevalence of 4% at age less than 40 years, and increases to 47% at age 70 years and older (Ravani *et al.* 2019). Several studies have similar finding that in the relationship between lipid profile and eGFR, total cholesterol does not have a significant relationship with eGFR (Palebangan *et al.* 2020; Zhang *et al.* 2019).

Dyslipidemia is an increase in cholesterol levels, Low Density Lipoprotein (LDL) or triglyceride levels, and decreased High Density Lipoprotein (HDL) levels. Moreover, most previous studies investigating the relationship between renal function and lipid profile have focused on specific types of dyslipidemia, such as High-Density Lipoprotein Cholesterol (HDL-C) (Herrington *et al.* 2016) and Low-Density Lipoprotein Cholesterol (LDL-C) (Chen *et al.* 2013).

A number of studies have revealed the role of dyslipidemia in the development of CKD.

Table 2. Categories of lipid profile, creatinine, blood sugar, and glomerular filtration rate of respondents

Lipid profile, creatinine, blood sugar, and glomerular filtration rate	n=893	%
Total cholesterol		
Normal (<200 mg/dL)	492	55.1
Upper limit (200–239 mg/dL)	312	34.9
High (≥240 mg/dL)	89	10.0
HDL		
Low (male <40 mg/dL; female <50 mg/dL)	385	43.1
High (male ≥40 mg/dL; female ≥50 mg/dL)	508	56.9
LDL		
Normal (<100 mg/dL)	187	21.0
Close to normal (100–129 mg/dL)	336	37.6
Upper limit (130–159 mg/dL)	277	31.0
High (160–189 mg/dL)	93	10.4
Triglyceride		
Normal (<150 mg/dL)	740	82.9
High limit (150–199 mg/dL)	101	11.3
High (200–449 mg/dL)	49	5.5
Very High (>449 mg/dL)	3	0.3
Creatinine		
High (male >1.2 mg/dL; female >1.0 mg/dL)	16	1.8
Normal (male 0.7–1.2 mg/dL; female 0.5–1.0 mg/dL)	870	97.4
Low (male <0.7 mg/dL; female <0.5 mg/dL)	7	0.8
Blood glucose		
Fasting blood glucose		
Normal (<100 mg/dL)	893	100.0
2-Hour glucose		
Normal (<140 mg/dL)	893	100.0
eGFR		
Normal eGFR (≥60 mL/minute/1.73 m^2)	877	98.2
Abnormal eGFR		
Mild to severe loss (30–59 mL/ minute /1.73 m^2)	4	0.5
Failure or close to failure (<15 mL/ minute /1.73 m^2)	12	1.3

eGFR: estimated Glomerular Filtration Rate; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein

However, the role of blood lipid types in the incidence and development of CKD seems to be contradictory. Several studies have results that contradict those found in this study. A study by Liang *et al.* (2020) concluded that high TC and TG are associated with decreased renal function and possibly an increased incidence of CKD in the general population, although the exact mechanism of how dyslipidemia may cause CKD is still under investigation. However, the current study suggests that an abnormal lipid profile in the blood leads to ectopic accumulation of lipids, which can occur in virtually any cell type, from mesangial cells to podocytes to proximal tubular epithelial cells. High lipid levels lead to mitochondrial damage and may also be more lethal to proximal tubular cells. High cholesterol levels can also cause macrophage infiltration and foam cell formation in the kidney. It is also believed that high levels of TC and LDL contribute to the risk of renal damage and dysfunction, even when TG levels are within the normal range.

Another study reported that High-Density Lipoprotein Cholesterol (HDL-C) was positively

Table 3. Relationship of age, sex, and lipid profile with eGFR

Variables	n	B	t	*p*
Age	893	-0.932	-22.467	<0.001
Sex	893	-1.418	-0.758	0.449
Total cholesterol	893	0.852	0.944	0.346
High-density lipoprotein	893	2.650	3.022	0.003
Low-density lipoprotein	893	-1.377	-2.197	0.028
Triglyceride	893	-1.479	-1.787	0.074

eGFR: Estimated Glomerular Filtration Rate; p-value based on statistical regression test, significantly at p<0.05

correlated with eGFR. Total Cholesterol (TC) and triglycerides were not correlated with eGFR. Low levels of HDL-C are an independent risk factor for the development of chronic kidney disease (Zhang *et al.* 2019).

In addition, a study conducted by McMahon *et al.* (2014) showed the accumulation and breakdown of triglyceride products from lipid metabolism in the blood of patients with CKD, where severe atherosclerotic conditions and pro-inflammatory effects on the vasculature in the kidney parenchyma occur. Previous studies have found that triglyceride levels increase and HDL-C levels decrease with decreasing GFR, while total cholesterol and LDL cholesterol levels tend to remain in the normal range (Herrington *et al.* 2016). Another study reported that Low-Density Lipoprotein Cholesterol (LDL-C) did not correlate with eGFR (Zhang *et al.* 2019).

In addition to low HDL and low eGFR, hypertriglyceridemia is also an early feature of renal failure. According to the study by Bhavsar, patients with impaired renal function show increased TG concentrations even though serum creatinine levels are within normal limits. The study mentioned that individuals with renal insufficiency usually show an abnormally elevated serum Triglyceride Level (TGL) after eating fatty foods (postprandial lipemia). An experimental study showed that the accumulation of TGL-rich lipoproteins (Very-Low-Density Lipoprotein (VLDL)), chylomicrons, and their remnants) in individuals with predialysis CKD is primarily due to a decrease in their catabolism. The most important pathophysiological mechanisms underlying the development of hypertriglyceridemia in renal failure are the downregulation of several gene expressions, changes in the composition of lipoprotein particles, and the direct inhibitory effect of various uremic toxins on enzymes involved in lipid metabolism. Besides HDL and TG, LDL is also involved in this process (Patel 2019). Our study has similar results with the study conducted by Bhavsar, that increase in LDL significantly affects the decrease in eGFR, which has the potential to cause CKD.

This study still has limitations. Despite the use of cross-sectional data analysis, other variables that may affect the glomerular filtration rate, such as diet, fluid intake, and physical activity, were not analyzed. It is necessary to perform the multivariate analysis that uses more variables of cohort data to obtain more valid results if these biomedical parameters are to be used as model predictors.

CONCLUSION

Dyslipidemia and respondent age have a significant relationship with the estimated Glomerular Filtration Rate (eGFR) in non-diabetic respondents. A decline in kidney function may also be the result of dyslipidemia condition.

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DECLARATION OF CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interest.

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