Dyslipidemia in Chronic Kidney Disease Patients at Dr. Soetomo Hospital Surabaya

Dislipidemia pada Pasien Penyakit Ginjal Kronis di RSUD Dr. Soetomo Surabaya

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Abstract
Epidemiological studies report that patients with chronic kidney disease (CKD) have a higher risk of mortality from cardiovascular disease than the general population. Previous studies have shown that dyslipidemia is thought to play a role in the development of atherosclerosis in patients with CKD. Dyslipidemia is known to be common in CKD patient population, but shows a diverse patterns in various CKD patient populations. This study aimed to analyze the lipid profile and lipid ratio in CKD patients at Dr. Soetomo Hospital Surabaya for the period 2016-2017. This cross-sectional study was conducted through retrospective observation of the medical records of CKD patient at the Kidney-Hypertension Polyclinic of Dr. Soetomo Hospital Surabaya in the 2016-2017 period. A total of 68 research subjects were analysed in this study. Most of the study subjects were male (68%) and the median age was 54 years. Almost 70% of the study subjects had CKD stage 5. Increased levels of total cholesterol and triglyceride were found in 37% of the study subjects. Meanwhile, a decrease in HDL-cholesterol levels and an increase in LDL-cholesterol and non-HDL-cholesterol levels were found in 60% of the study subjects. The mean value of total cholesterol, LDL-cholesterol, and non-HDL-cholesterol levels in the female group was significantly higher based on statistical calculations ($p<0.05$). Most of the study subjects were predicted to be at risks for developing cardiovascular disease based on the calculation of several lipid ratios. The incidence of dyslipidemia in population is known to be higher than in the general population. Decreased HDL-cholesterol, increased LDL-cholesterol, and non-HDL-cholesterol are the most common forms of dyslipidemia in population studies.

Keywords : cardiovascular disease; chronic kidney disease; lipid profiles; lipid ratios

Abstrak
Studi epidemiologi melaporkan bahwa pasien penyakit ginjal kronis memiliki risiko mortalitas akibat penyakit kardiovaskular yang lebih tinggi dibandingkan populasi umum. Studi sebelumnya menunjukkan bahwa dislipidemia diduga turut berperan terhadap terjadinya atherosklerosis pada pasien penyakit ginjal kronis. Dislipidemia diketahui umum ditemukan pada populasi pasien penyakit ginjal kronis namun menunjukkan pola yang bervariasi pada berbagai populasi pasien penyakit ginjal kronis. Studi ini bertujuan untuk menganalisis profil lipid dan rasio lipid pada pasien penyakit ginjal kronis di RSUD Dr. Soetomo Surabaya periode 2016-2017. Studi cross-sectional ini dilakukan melalui pengamatan retrospektif terhadap catatan rekam medis pasien penyakit ginjal kronis di Poliklinik Ginjal-Hipertensi

RSUD Dr. Soetomo Surabaya pada periode 2016-2017. Sebanyak 68 subjek penelitian dianalisis dalam penelitian ini. Sebagian besar subjek penelitian berjenis kelamin laki-laki (68%) dan nilai median usia pada subjek penelitian mencapai 54 tahun. Sebagian besar subjek penelitian memiliki penyakit ginjal kronis stadium 5 (70%). Peningkatan kadar kolesterol total dan trigliserida ditemukan pada sekitar 37% subjek penelitian. Sedangkan, penurunan kadar HDL-kolesterol dan peningkatan kadar LDL-kolesterol serta non HDL-kolesterol ditemukan pada sekitar 60% subjek penelitian. Nilai rerata kadar kolesterol total, LDL-kolesterol, dan non HDL-kolesterol pada kelompok berjenis kelamin perempuan secara signifikan lebih tinggi berdasarkan perhitungan statistika (p<0.05). Sebagian besar subjek penelitian diprediksi memiliki risiko untuk mengalami penyakit kardiovaskular berdasarkan perhitungan beberapa rasio lipid. Insiden dislipidemia pada studi populasi diketahui lebih tinggi dibandingkan populasi umum. Penurunan HDL-kolesterol, peningkatan LDL-kolesterol, dan non HDL-kolesterol merupakan bentuk dislipidemia yang paling umum ditemukan pada studi populasi.

Kata kunci : penyakit ginjal kronis; penyakit kardiovaskular; profil lipid; rasio lipid

INTRODUCTION

Chronic kidney disease (CKD) is a multisystem disorder that caused abnormalities to kidney structures and caused progressive loss of kidney functions over the course of time. It's characterized by glomerular filtration rate less than 60 ml/min/1.73 m^2 or by the presence of a marker of kidney damages for more than three months.[1] CKD affected about 8% to 16% of world population.[2] This prevalence is predicted to rise in the course of time due to increased incidence of diabetes mellitus and hypertension in the population as the main risk factor of CKD.[3,4] CKD became one of major health problems in the world due to high morbidity and mortality rate.

Recent epidemiological studies reported that CKD patients have higher morbidity and mortality risk due to cardiovascular disease than the general population.[5] Cardiovascular disease in CKD patients was basically driven by two principal mechanisms, i.e. non-atherosclerotic and atherosclerotic processes.[6] Previous studies suggested that dyslipidemia may contribute to the development of atherosclerotic cardiovascular disease (ASCVD) in CKD patients.[7] Abnormalities of lipid and lipoprotein metabolisms induced by uremic toxin or proteinuria were thought to be one of the underlying causes of dyslipidemia in CKD patients.[8] Recent studies reported that dyslipidemia was frequently found in CKD patient population but not universally found.[9] The lipid profiles of chronic kidney disease patients also showed various patterns depend on nutritional status, degree of kidney functions and proteinuria, etc.[10] The lipid profiles may be useful indicators for practitioners to predict atherosclerotic cardiovascular disease in chronic kidney disease patients. Recent studies also reported that lipid ratios may be the superior indicators for predicting atherosclerotic cardiovascular disease than the independent lipid level.[11]

There are limited study on the lipid profiles and associated cardiovascular risk incident according to lipid ratios of CKD patient's population in Indonesia, whereas the study could be useful to decrease morbidity and mortality of CKD patients due to cardiovascular events. Therefore, lipid profiles and lipid ratios of CKD patients needs to be further explored in Indonesia population. The aim of the current study was to analyze the lipid profiles and lipid ratios of chronic kidney disease patients in Dr. Soetomo General Hospital Surabaya Indonesia.

METHODS

This cross-sectional study was conducted from retrospective searches of medical databases at Renal and Hypertension Outpatient Clinic of Dr. Soetomo General Hospital in Surabaya Indonesia. The medical databases of patients with chronic

kidney disease admitted to clinic from 2016 to 2017 were collected for the study. Diagnosis of CKD was established based on KDIGO 2012 guildelines.[1] Records of CKD patients with age over 18 years old, complete general laboratory examination (i.e. lipid profiles, serum creatinine, Blood Urea Nitrogen (BUN)) were included. Patients who were pregnant, had renal transplant and those on lipid lowering medications, steroid or immunosuppresants were excluded from the study. Sample size was established using an equation based on population parameters, which indicated a minimum of 61 subjects, based on the mean prevalence of approximately 20% reported in previous studies, statistical significance of 5% (z=1.96), and precision of 10%.[12,13] Total 68 subjects were included in the study. The study has been approved by Health Research Ethics Committee of Dr. Soetomo General Hospital with Recommendation Number 134/Panke.KKE/II/2017.

The current study described clinical characteristics, lipid profiles, and lipid ratios of the study population. Clinical characteristics (i.e. age, gender, stage of CKD, creatinine serum, BUN) and lipid profiles ((i.e. total cholesterol, triglyceride, High Density Lipoprotein (HDL)-cholesterol, Low Density Lipoprotein (LDL)-cholesterol, non HDL-cholesterol) were obtained secondarily from the medical records. Creatinine serum, BUN, and lipid profiles data included in the study were derived from the results of laboratory examination conducted in Dr. Soetomo Hospital which were taken at the same period.

The stage of CKD was determined by glomerular filtration rate (GFR) which estimated using CKD-EPI formula by submitting four variables (i.e. age, gender, race, and creatinine serum level) into the equation of CKD-EPI.[1] CKD stage 1 defined when GFR ≥90 mls/min with evidence of kidney damage, stage 2 (GFR 60–89 mls/min with evidence of kidney damage), stage 3 (GFR =30–59 mls/min with or without evidence of kidney damage), stage 4 (GFR =15–29 mls/ min with or without evidence of kidney damage) and stage 5 (GFR < 15mls/min with or without evidence of kidney damage or already had renal replacement therapy)[1]. Non HDL-cholesterol was determined by subtraction of total cholesterol level and HDL-cholesterol level. Dyslipidemia was defined as any or a combination of the following: TC >200 mg/dl, HDL-C <50 mg/dl in females and <40 mg/dl in males, LDL-C >130 mg/dl and TG > 150mg/dl.[14,15] Lipid ratios were calculated by dividing two lipid variables (i.e. total cholesterol to HDL-cholesterol (TC/HDL-C), triglyceride to HDL-cholesterol (TG/HDL-C), LDL-cholesterol to HDL-cholesterol (LDL-C/HDL-C), non HDL-cholesterol to HDL-cholesterol (non HDL-C/HDL-C), and the transformation logarithm of triglyceride to HDL-cholesterol ratio (log(TG/HDL-C)). The cutoff values for TC/HDL-C is 3.5, LDL-C/HDL-C 3.0, non HDL-C/HDL-C 3.25, TG/HDL-C 3.5, and log-TG/HDL-C -0.3.[16-19] Comparison of clinical characteristics, lipid profiles, and lipid ratios based on CKD stage and gender group was also conducted in the current study.

SPSS version 16.0 was used for statistical analysis. Results of the study were presented in tabular forms. Categorical variables (i.e.gender and CKD stage) were presented as frequency and percentage. Continuous variables (i.e. age, serum creatinine, BUN, e-GFR, lipid profiles, lipid ratios) were presented as mean and standard deviation for normally distributed data. Continuous variables with skewed distributed data were presented as median and interquartil range. Comparison of clinical characteristics, lipid profiles, and lipid ratios based on CKD stage and gender group was examined using Student's t test for normally distributed data and Mann Whitney U test for skewed distributed data. P value <0.05 was considered statistically significant.

RESULTS

A total of 68 subjects was included in the analysis. Most subjects were men (68%) and the median age was 54 years. Most subjects were CKD patient's stage 5 (70%). The median of total cholesterol and triglyceride levels in the subjects were relatively normal as shown in Table 1.

Table 1. Clinical Characteristics, Lipid Profiles, and Lipid Ratios of Study Population Based on Gender

	Total (n = 68)	**Male Group (n = 46)**	**Female Group (n = 22)**	***p* value**
Age (years)	54 (46 – 61)[a]	5312[b]	52 11	0.81[c]
SC (mg/dL)	7.84 5.33	7.97 5.70	7.56 4.55	0.77[c]
eGFR(ml/min/1.73m^2	8 (4 –18)	10 (4 – 22)	6 (3 – 11)	0.17[d]
BUN (mg/dL)	57 34	56 35	60 31	0.65[c]
Lipid profiles				
TC (mg/dL)	193 60	178 51	224 67	0.003[c]
TG (mg/dL)	127 (80 – 173)	128 80	207 186	0.07[c]
HDL-C (mg/dL)	42 15	41 16	44 13	0.54[c]
LDL-C (mg/dL)	118 40	112 36	132 45	0.05[c]
Non HDL-C (mg/dL)	151 71	137 46	180 68	0.01[c]
Lipid ratios				
TC/HDL-C	5.00 2.00	4.73 1.70	5.56 2.46	0.11[c]
TG/HDL-C	2.97 (1.77–4.90)	3.64 2.82	5.75 6.76	0.17[c]
LDL-C/HDL-C	3.12 1.40	3.06 1.40	3.25 1.41	0.59[c]
Non HDL-C/HDL-C	4.00 2.00	3.73 1.70	4.56 2.46	0.11[c]
log(TG/HDL-C)	0.13 0.34	0.09 0.32	0.22 0.37	0.12[c]

[a] Median (Quartil 1 – Quartil 3), [b] Mean Standard Deviation
[c] Student's t test was performed, [d] Mann Whitney U test was performed
CKD: Chronic Kidney Disease, BUN: Blood Urea Nitrogen, eGFR: estimated Glomerular Filtration Rate, HDL-C: High Density Lipoprotein-Cholesterol, LDL-C: Low Density Lipoprotein-Cholesterol, SC: Serum Creatinine, TC: Total Cholesterol, TG: Triglyceride.

Table 2. Clinical Characteristics, Lipid Profiles, and Lipid Ratios of Study Population Based on CKD Stage

	Total (n = 68)	**CKD stage 1-4** (n = 21)	**CKD stage 5** (n = 47)	***p* value**
Age (years)	54 (46 – 61)[a]	57 (50 – 63)	54 (41 – 59)	0.12[c]
Gender (%)	Male (67.6%) Female (32.4%)	Male (81.0%) Female (19.0%)	Male (61.7%) Female (38.3%)	
SC (mg/dL)	6.70 (3.58–12.06)	2.19 (1.61 – 3.36)	8.94 (5.9 – 13.35)	<0.001[c]
eGFR(ml/min/1.73m^2	8 (4 –18)	31 (20 - 42)	5 (3 – 9)	<0.001[c]
BUN (mg/dL)	53 (30 – 75)	19 (15 – 33)	66 (49 – 82)	<0.001[c]
Lipid profiles				
TC (mg/dL)	181 (153 – 216)	190 (158 – 232)	181 (148 – 215)	0.57[c]
TG (mg/dL)	127 (80 – 173)	150 (78 –178)	126 (81 – 172)	0.78[c]
HDL-C (mg/dL)	40 (30 – 50)	44 (34 – 50)	36 (30 – 48)	0.39[c]
LDL-C (mg/dL)	118 40[b]	120 38	118 41	0.86[d]
Non HDL-C (mg/dL)	138 (117 – 174)	155 (120 – 184)	137 (116 – 169)	0.51[c]
Lipid ratios				
TC/HDL-C	4.46 (3.51 – 6.30)	4.42 (3.55 – 6.34)	4.50 (3.30 – 6.30)	0.93[c]
TG/HDL-C	2.97 (1.77 – 4.90)	3.09 (1.67 - 5.60)	2.96 (1.83 – 4.90)	0.84[c]
LDL-C /HDL-C	3.12 1.40	3.02 1.36	3.17 1.42	0.69[d]
Non HDL-C/HDL-C	3.46 (2.51 – 5.30)	3.42 (2.55 – 5.34)	3.50 (2.30 – 5.30)	0.93[c]
log(TG/HDL-C)	0.13 0.34	0.14 0.36	0.13 0.33	0.95[d]

[a] Median (Quartil 1 – Quartil 3), [b] Mean Standard Deviation
[c] Mann Whitney U test was performed, [d] Student's t test was performed
CKD: Chronic Kidney Disease, BUN: Blood Urea Nitrogen, eGFR: estimated Glomerular Filtration Rate, HDL-C: High Density Lipoprotein-Cholesterol, LDL-C: Low Density Lipoprotein-Cholesterol, SC: Serum Creatinine, TC: Total Cholesterol, TG: Triglyceride.

The mean of LDL-cholesterol and the median of non HDL-cholesterol levels were slightly higher than normal limit. The median of HDL-cholesterol level in the study subjects was in the borderline. Thirty seven percent (37%) of study subjects showed elevation of total cholesterol and triglyceride levels and about 60% of study subjects showed the decline of HDL-cholesterol, elevation of LDL-cholesterol and non-HDL-cholesterol levels. All lipid ratios of study subjects were higher than cutoff values adapted from previous studies, except TG/HDL-C ratio. All lipid profiles and lipid ratios of female group were relatively higher than male group, but only the mean of total cholesterol, LDL-cholesterol, and non HDL-cholesterol levels were statistically significant ($p<0.05$).

The median age and men proportion of CKD stage 1-4 group was higher than CKD stage 5 group. Serum creatinine and BUN levels of CKD stage 1-4 group were significantly lower than CKD stage 5 group and eGFR of CKD stage 1-4 group was significantly higher ($p<0.001$). All lipid profiles of CKD stage 1-4 group were relatively higher than CKD stage 5 group, but not statistically significant ($p>0.05$). All lipid ratios of CKD stage 5 group were relatively higher than CKD stage 1-4 group, except TG/HDL-C and log (TG/HDL-C). Nevertheless, none of those differences were statistically significant ($p>0.05$) as shown in Table 2.

DISCUSSION

The median age of CKD patients in the study subjects was relatively lower than the results of previous studies in Indonesia. showed that the highest prevalence of CKD patients was in the age over 75 years.[12] However, about 70% of the study subjects were in the age over 50 years. The results of this study seem to be quite consistent with previous studies which reported that CKD patients commonly occurred in the elderly population.[20,21] The high incidence of diabetes mellitus and hypertension (as major risk factors of CKD) in addition to the physiological decline of renal function in elderly may lead to higher incidence of CKD in the elderly population.[22-24] Most study subjects were men, which apparently consistent with the results of previous large-scale study with population of CKD patient in Indonesia.[12] Previous studies hypothesized that testosterone may contribute to the pathogenesis of CKD, whereas estrogen was suggested to have protective effects on CKD.[25,26] But the studies are still controversial because the results were not consistent. Most study subjects were CKD patients in stage 5 (70%). This situation may reveal the fact that CKD patients in Indonesia tend to have health care seeking habit in advanced stage.

The median of total cholesterol and triglyceride levels in the study subjects were relatively normal. This result was consistent with previous studies reported that CKD patients tend to have normal cholesterol levels.[8] Although the median of triglyceride level was within normal limit, the incidence of hypertriglyceridemia in the study subjects (37%) was relatively higher than general in Indonesia (24.9%) and US (29.6%) population.[12,27] Impaired clearance of triglyceride rich lipoprotein (VLDL, chylomicron, and the remnants) due to decreased LPL, hepatic lipase, VLDL receptors, hepatic ACAT, LRP activity, and HDL metabolic disorders was estimated to cause the elevation of triglyceride levels in CKD patients.[8] The study subjects showed slightly increased LDL-cholesterol levels in spite of previous studies which reported that CKD patients tend to have normal levels of LDL-cholesterol.[8] But, previous studies reported that heavy proteinuria might induce elevation of LDL-cholesterol levels in CKD patients.[8]

The decrease of HDL cholesterol level in the study subjects was about 59%, which was relatively higher than the decrease of HDL cholesterol level in Indonesia and US general population, which only reached 23%.[12,27] The decrease of HDL-cholesterol level in patients with CKD was estimated caused by the decline of LCAT activity (induced by uremic toxin) and apoAI (as LCAT enzyme activator) that mediates HDL to take cholesterol away from extra-hepatic tissue.[8] The increased of CETP and ACAT activity was also estimated to cause the decline of HDL-

cholesterol levels in CKD patients.[8] The mean of non HDL-C level in the study subjects was higher than normal limit. The elevation of non HDL-cholesterol in the study subjects was about 63%, which relatively higher than the incidence in the US general population (13%).[27] Although total cholesterol levels in the study subjects were relatively normal, the decline of HDL-cholesterol levels may cause the increase of non HDL-cholesterol levels in the study subjects. Non HDL-cholesterol was known to be associated with the incidence of coronary heart disease in general and CKD patient population.[28-30] This may associate with the ability of non HDL-cholesterol to reflect the overall atherogenic particles (i.e. Lp(a), LDL, IDL, VLDL, chylomicron, and the remnants).[15] Thus, the high level of non HDL-cholesterol in the study subjects may reflect the high risk incidence of ASCVD in the study subjects.

Lipid ratio (also known as atherogenic index) is estimated to have higher predictive capacity for cardiovascular disease risk than independent lipid component.[11] All lipid ratios of the study subjects were higher than cutoff values, except TG/HDL-C ratio. TC/HDL-C and LDL-C/HDL-C ratios were known to predict the incidence of coronary heart disease in general population much better than the independent lipid profile.[11,17] However, use of TC/HDL-C ratio is more recommended for individuals with triglyceride levels exceeding 300 mg/dL because the cholesterol components in the VLDL particles are increasing at this levels.[11] Previous studies reported that non HDL-C/HDL-C ratio was similar to apoB/apo-A1 ratio to predict the incidence of coronary heart disease in CKD patient population as well as in the general population.[31] Log(TG/HDL-C) or known as AIP (atherogenic index plasma) is analogous to the TG/HDL-C ratio, but the logarithmic transformation of this ratio serves to qualify the statistical normality standards. Previous research reported that AIP reflects the contents of small LDL and small HDL, which known as atherogenic components.[32] AIP is known to be a sensitive predictor of the incidence of atherosclerosis and the risk of cardiovascular disease.[31] Thus, the higher lipid ratios of the study subjects than cutoff values may indicate the higher risk incidence of ASCVD in the study population.

All lipid profiles and lipid ratios (except TG/HDL-C and AIP) of CKD stage 1-4 group were relatively higher than CKD stage 5 group, but none of those differences were statistically significant ($p>0.05$). All lipid profiles and lipid ratios of female group were relatively higher than male group, but only total cholesterol, LDL-cholesterol, and non HDL-cholesterol levels were statistically significant ($p>0.05$). These results were quite consistent with previous studies showed that dyslipidemia was more prevalent in women, especially in post-menopausal women.[33,34] The median age of women's group in the study subjects was 52 years old, which apparently belong to the menopausal age. Previous studies also reported that elevation of total cholesterol and LDL-cholesterol levels were the most common features of dyslipidemia in post-menopausal women, which apparently quite consistent with the results of this study.[33,34] The elevation of total cholesterol levels may also increase the levels of non HDL-cholesterol. Previous studies suggested that lack of estrogen due to decreased ovarian function played important role in the mechanisms of dyslipidemia in post-menopausal women.[33,34]

There are some limitations in this study. This is a retrospective research which may be insufficient to control the confounded variables that can influence the results of the study. This research data was taken by cross-sectional method, so that the actual state of the patients may less described by this research. Data about etiology, comorbid, and proteinuria of the patients were not taken whereas those variables may influence the incidence of dyslipidemia in the study population. Researchers excluded subjects whose took lipid lowering agents, steroid, or immunosuppresants in order to mitigate bias in the current study.

CONCLUSION

The incidence of dyslipidemia in the study population was relatively higher than the general population. The decline of HDL-cholesterol, elevation of LDL-cholesterol and non HDL-cholesterol levels were the most common features of dyslipidemia that found in the study population. Most study subjects were predicted to have the risks of ASCVD based on the calculation of some lipid ratios, so that research about the effect of lipid profiles on the incidence of ASCVD in CKD patients need to be developed for further studies.

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