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THE CORRELATION BETWEEN PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 LEVELS AND LOW-DENSITY LIPOPROTEIN LEVELS IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Introduction: Chronic kidney disease (CKD) patients have an increased mortality rate when accompanied by cardiovascular disease due to dyslipidemia. Elevated PCSK9 levels in CKD lead to increased LDL cholesterol. This study aims to evaluate the correlation between PCSK9 levels and serum LDL cholesterol in CKD patients.
Methods: This observational analytical study used a cross-sectional approach. Subjects were patients with CKD aged 18-59 years who were treated at the Inpatient Installation of the Internal Medicine Department of RSUP Dr. M. Djamil Padang. Statistical analysis was performed using SPSS.
Results: The study included 30 CKD patients, of whom 56.6% were male. The average age was 50.03 (6.7) years, with a BMI of 23.12 kg/m² (5.1). Obesity was found in 40% of the sample. Average cholesterol was 169.3 (60.13) mg/dL, HDL cholesterol was 29.03 (14.15) mg/dL, triglycerides were 185.13 (82.4) mg/dL, and creatinine was elevated at 9.2 (5.15) mg/dL. Average glomerular filtration rate below 15 mL/min/1.73 m² was 9.55 (9.38) mL/min. Most patients had CKD stage 5 (83.33%). The data showed a weak, statistically insignificant positive correlation ($r=0.011$, $p>0.05$) between serum PCSK9 levels and LDL cholesterol in CKD patients.
Conclusion: No significant correlation was found between PCSK9 levels and serum LDL cholesterol in CKD patients. This suggests that other factors may play a more dominant role in LDL regulation in CKD, and further research is needed to explore these mechanisms.
Keywords : LDL Cholesterol., PCSK9., Chronic Kidney Disease

INTRODUCTION

Chronic kidney disease (CKD) is characterized by a decline in kidney function or structural abnormalities in the kidneys persisting for more than three months.[1] This decline in kidney function is indicated by a Glomerular Filtration Rate (GFR) less than 60 ml/min per 1.73 m^2.[2] According to the Indonesian Society of Nephrology (PERNEFRI), the incidence of CKD in Indonesia in 2018 was 66,433 patients, which is double the number from the previous year.[3] Meanwhile, the prevalence of CKD patients in West Sumatra accounts for 0.2% of the total CKD cases in Indonesia.[3]

According to the Basic Health Research (RISKESDAS) report, the prevalence of CKD is 0.38% of the total population, which equates to 713,783 individuals suffering from CKD. The incidence of CKD has increased from 2013 to 2018. The highest numbers of CKD patients undergoing hemodialysis are found in Jakarta (38.71%), Bali (37.04%), and West Sumatra (15%).[4] In RSUP Dr. M. Djamil Padang, in 2017, there were 7,801 outpatient and 911 inpatient CKD patients, with 6,472 undergoing hemodialysis. This represents a significant increase compared to the incidence of CKD in 2016, which included 2,937 outpatient and 586 inpatient patients, with 2,107 undergoing hemodialysis.[5]

Chronic kidney disease increases the risk of mortality due to cardiovascular abnormalities. One of the pathogenesis mechanisms for cardiovascular disorders in CKD patients is the accelerated formation of atherosclerotic plaques due to dyslipidemia, uremic toxins, inflammation, oxidative stress, and endothelial dysfunction.[6] An important factor in these cardiovascular abnormalities is the elevated level of Low-Density Lipoprotein (LDL).

Increased LDL levels in CKD patients may be influenced by Proprotein Convertase Subtilisin/Kexin 9 (PCSK9). PCSK9 is an enzyme that plays a significant role in lipid metabolism, acting as a primary regulator of LDL degradation. PCSK9 is involved in both intracellular and extracellular lipoprotein metabolism.[7] In CKD, high levels

of PCSK9 are observed due to increased inflammatory factors such as TNF α, which enhance protein expression in HepG2 cells and induce messenger Ribonucleic Acid (mRNA) PCSK9.[8] Based on this background, this study aims to analyze the correlation between PCSK9 levels and LDL in CKD patients to better understand the role of PCSK9 in lipid metabolism disorders associated with CKD.

METHODS

This study is observational analytical research with a cross-sectional approach. The research was conducted at the Inpatient Installation of the Internal Medicine Department of RSUP Dr. M. Djamil Padang.

The sample recruitment process in this study was conducted among patients with chronic kidney disease who were receiving treatment at the Inpatient Ward of Internal Medicine and the Outpatient Clinic of Internal Medicine at Dr. M. Djamil Central General Hospital, Padang. The target population consisted of patients aged 18 to 59 years. From this population, samples were selected based on predetermined inclusion and exclusion criteria. The inclusion criteria included patients diagnosed with stage 3 to 5 chronic kidney disease, aged between 18 and 59 years, and willing to participate by signing an informed consent form. The exclusion criteria included patients who had undergone renal replacement therapy, patients with sepsis, suspected hepatitis C, acute coronary syndrome, thyroid disorders, liver cirrhosis, corticosteroid use, pregnancy, statin use, and those receiving protease inhibitor therapy. Sampling was carried out using consecutive sampling, in which all eligible subjects who met the criteria were recruited throughout the study period until the required sample size was achieved. Based on the formula used, the minimum required sample size was calculated to be 29.020, which was then rounded up to 30 samples.

The collected data were analyzed statistically using SPSS. The study has received ethical clearance from the Research Ethics Committee of RSUP Dr. M Djamil Padang. Patients were informed about the research objectives and the procedures involved. Patient identities will remain confidential. Those who consented to participate in the study signed an informed consent form.

RESULTS

The study included 30 CKD patients, of whom 56.6% were male. The average age was 50.03 (6.7) years, with a BMI of 23.12 kg/m² (5.1). Obesity was found in 40% of the sample. Average cholesterol was 169.3 (60.13) mg/dL, HDL cholesterol was 29.03 (14.15) mg/dL, triglycerides were 185.13 (82.4) mg/dL, and creatinine was elevated at 9.2 (5.15) mg/dL. Average glomerular filtration rate below 15 mL/min/1.73 m² was 9.55 (9.38) mL/min. Most patients had CKD stage 5 (83.33%) (Table 1).

Table 1. Study Characteristics

Characteristic	n (%)	Mean (SD)
Gender		
Male	17 (56.6)	
Female	13 (43.4)	
Age (years)		50.03 (6.7)
18-40	3 (10)	
41-59	27 (90)	
BMI (kg/m²)		23.12 (5.1)
< 18.5 (underweight)	4 (13.3)	
18.5-22.9 (normal)	6 (20)	
23-24.9 (overweight)	8 (26.7)	
≥ 25 (obesity)	12 (40)	
Total Cholesterol (normal: <200 mg/dL)		169.3 (60.13)
HDL Cholesterol (normal: >40 mg/dL)		29.03 (24.15)
Triglycerides (normal: <150 mg/dL)		185.13 (82.4)
Creatinine (normal: 0.6-1.2 mg/dL)		9.2 (5.1)
GFR (mL/min/1.73 m²)		9.55 (9.38)
30-59 (Stage 3)	1 (3.33)	
15-29 (Stage 4)	4 (13.3)	
< 15 (Stage 5)	25 (83.33)	

Characteristic	n (%)	Mean (SD)
Comorbidities		
Type 2 DM + Hypertension + Heart Failure + Pneumonia + Anemia	3 (10)	
Type 2 DM + Hypertension + Heart Failure + Pneumonia	3 (10)	
Type 2 DM + Hypertension + Heart Failure + Anemia	3 (10)	
Type 2 DM + Hypertension + Pneumonia + Anemia	1 (3.33)	
Type 2 DM + Heart Failure + Pneumonia + Anemia	2 (6.67)	
Type 2 DM + Hypertension + Heart Failure	2 (6.67)	
Type 2 DM + Hypertension + Anemia	4 (13.3)	
Type 2 DM + Heart Failure + Anemia	3 (10)	
Type 2 DM + Heart Failure + Pneumonia	2 (6.67)	
Type 2 DM + Heart Failure	3 (10)	
Type 2 DM + Pneumonia	1 (3.33)	
Type 2 DM + Anemia	2 (6.67)	
Type 2 DM	1 (3.33)	

The median serum PCSK9 level was 36.87 ng/mL, and the median serum LDL cholesterol level was 94.0 mg/dL. There was a weak, statistically insignificant positive correlation ($r=0.011$, $p>0.05$) between serum PCSK9 levels and LDL cholesterol in CKD patients. (Table 2, Figure 1).

Table 2. PCSK9 and Serum LDL Cholesterol Levels in CKD Patients

Variable	n (%)	Median (Min-Max)
PCSK9 serum (ng/mL)	30	36.87 (12.08-94.45)
Serum LDL Cholesterol (mg/dL)	30	94.0 (47.0-284.00)
< 100 mg/dL	17 (56.67)	
≥ 100 mg/dL	13 (43.33)	

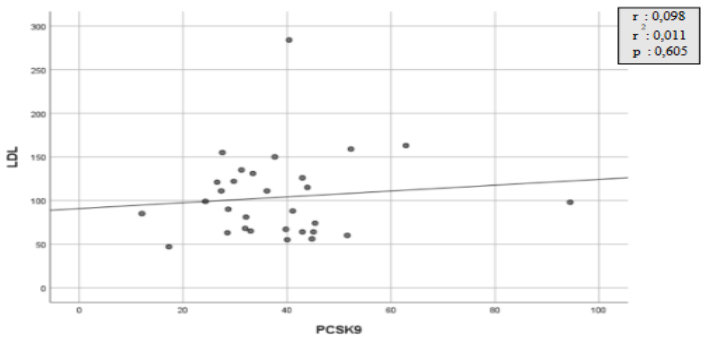

Figure 1. Correlation Graph Between PCSK9 Levels and LDL Cholesterol in Patients with Chronic Kidney Disease. (Source: Author, 2024)

DISCUSSION

From the study characteristics, it was found that the number of males is higher than that of females, with 17 male patients (56.6%) and 13 female patients (43.4%). Several studies have shown similar results. In a study by Praramadhan et al. it was found that there were more male patients than female patients (54.5% vs. 45.5%).[9] Khatiwada et al. at Koirala Institute of Health Sciences, Dharan, Nepal, found that 53.8% of patients were male and 46.2% were female[8]. According to the Basic Health Research (Riskesdas) and Indonesian Renal Registry (IRR), the prevalence of chronic kidney disease (CKD) in Indonesia is higher in males (0.3%) compared to females (0.2%). Data from the Centers for Disease Control (CDC) 2021 in the United States indicate that kidney failure is higher in women (14%) compared to men (12%).[10] According to a study by Carrero JJ et al., CKD prevalence is generally higher in women than in men. In some countries, the prevalence of CKD in women is twice as high as in men, such as in France, Thailand, Portugal, and Turkey. The prevalence of men compared to women is only found in Japan and Singapore.[11] There is an estrogen protective effect that has anti-fibrotic and anti-apoptotic effects on the kidneys. Women with CKD have a longer life expectancy compared to men with CKD. In men, testosterone has effects that increase angiotensin II activation and have pro-inflammatory, pro-apoptotic, and pro-fibrotic effects on the kidneys. Men are also more likely to have unhealthy lifestyles compared to women. Men with CKD often have poor eating habits and generally do not adhere to the dietary restrictions specific to CKD patients.[12]

Sex can affect PCSK9 and LDL cholesterol levels. According to Levenson AE et al., the mechanism underlying sex differences in PCSK9 levels is still unclear, but most studies suggest that estrogen suppresses PCSK9 levels. High-dose estradiol treatment suppresses hepatic PCSK9 expression in mice.[13] Ooi TC et al., reported that circulating PCSK9 levels are not related to and not affected by testosterone in men, while in women, estradiol levels are inversely related to circulating PCSK9 levels. Mice treated with high-dose estradiol can reduce PCSK9 gene expression by 45%.[14]

Several studies have shown that age can affect PCSK9 and LDL cholesterol levels. In our study, the most common age group was 41-59 years (90%). These results are similar to those of Saini M et al. in India, which found that the average CKD patient age in the largest age group was 41-60 years, with an average age of 44.02.[15] Nearly the same as the study by Adejumo et al., which found an average age of 46.98 years.[16] Kumari et al. also found that the average age of CKD patients was 45.28 years.[17]

Older age is associated with more comorbidities. Older age is also linked with lower physical activity, higher obesity incidence, and poor diet quality, which leads to insulin resistance and high LDL cholesterol levels.[18] PCSK9 levels are higher in postmenopausal women compared to premenopausal women and are inversely correlated with estrogen levels. Estrogen increases PCSK9 phosphorylation and decreases PCSK9's ability to lower LDL receptors. PCSK9 can disrupt LDL receptor accumulation on the plasma membrane in the absence of estrogen.[19]

The average creatinine level in this study is 9.2 (5.1) mg/dL, and the average glomerular filtration rate (GFR) is 9.55 (9.38) mL/min/1.73 m².[20] This is similar to the study by Senge et al. on the relationship between serum lipid levels and GFR values in CKD. In this study, the average creatinine level was 7.87 mg/dL, with an average GFR of 7.37 mL/min/1.73 m². This study found the highest prevalence of stage 5 CKD at 83.33%. Serum PCSK9 concentration can significantly increase in kidney failure patients with conservative therapy. Serum PCSK9 levels are negatively correlated with glomerular filtration rate. Progressive loss of kidney function leads to uremia. In uremia, the binding between PCSK9 and LDL receptors is disrupted. High PCSK9 gene expression in kidney failure is triggered by systemic inflammation in CKD.[21]

The PCSK9 levels in patients with chronic kidney disease vary depending on the comorbidities and exclusion criteria of each study. In this study, the median serum PCSK9 level is 36.87 ng/mL, with a minimum value of 12.08 ng/mL and a maximum value of 94.45 ng/mL. This

value is similar to the average PCSK9 level found in the study by Hwang et al., which reported an average PCSK9 level of 36.6 ng/mL.[22] In this study, exclusion criteria included pregnancy and malignancy. The study by Kajingulu FP et al. in Congo, which examined PCSK9 levels in CKD patients, found an average PCSK9 level of 28.0 ng/ml.[23] The study by Jin K on PCSK9 in CKD patients without renal replacement therapy reported an average PCSK9 level of 15.13 ng/mL. This study excluded patients under 18 years old, those with chronic liver disease, malignancy, and infection within the past 4 weeks. PCSK9 was measured in a fasting state.[24]

Differences in PCSK9 levels across studies can be attributed to varying inclusion and exclusion criteria. Additionally, the use of different assay kits can affect PCSK9 levels due to differences in assay sensitivity. In this study, patients fasted for at least 10 hours. PCSK9 levels should be measured at specific times, such as in the morning after an overnight fast, to obtain an accurate comparison between cholesterol and PCSK9 levels.[25,26] PCSK9 serum levels exhibit a diurnal rhythm similar to cholesterol synthesis, with hepatic cholesterol synthesis peaking at night.

Fasting can reduce PCSK9 levels, with an 18-hour fast reducing serum PCSK9 by 35%. A fasting period of 2-7 days can lead to a 70-80% decrease in serum PCSK9 levels. PCSK9 expression is regulated by Sterol Regulatory Element-Binding Protein (SREBP), which is activated when intracellular free cholesterol levels decrease. Human PCSK9 levels exhibit a diurnal rhythm similar to cholesterol biosynthesis.[26] Dounousi E et al. noted that in CKD patients, PCSK9 levels are directly associated with increased sICAM-1 levels, which are a risk factor for cardiovascular disease in CKD patients. Inflammation, oxidative stress, and endothelial dysfunction play roles in the occurrence of cardiovascular disease. The study found that soluble Intercellular Adhesion Molecule-1 (sICAM-1) levels are directly related to PCSK9 levels in CKD patients.[27]

In this study, the median serum LDL cholesterol level was found to be 94.0 mg/dL, with a minimum value of 47 mg/dL and a maximum value of 284 mg/dL. This result is similar to the study by Saini et al., which reported an average LDL cholesterol level of 101.94 mg/dL in CKD patients[13]. The study by Bauer et al. in Germany found an average LDL cholesterol level of 106.3 mg/dL in 3,514 CKD patients.[28] Singh et al. in India reported an average LDL cholesterol level of 153.66 mg/dL in CKD patients.[18]

LDL cholesterol levels are also influenced by PCSK9. Proprotein convertase subtilisin/kexin type 9 can affect LDL cholesterol levels by 7%.[29] In adults, every 100 ng/mL increase in PCSK9 concentration will raise LDL cholesterol by 3.6 – 4.5 mg/dL. Elevated PCSK9 levels can reduce LDL receptors, leading to increased LDL cholesterol. In this study, the median PCSK9 level did not exceed 100 ng/mL, with a median of 36.87, a minimum of 12.08, and a maximum of 94.45 ng/mL, indicating that PCSK9 levels had minimal impact on serum LDL cholesterol in this study.[25]

Our study evaluated the correlation between PCSK9 levels and serum LDL cholesterol in patients with chronic kidney disease. A weak correlation was found between PCSK9 levels and LDL cholesterol in these patients ($r = 0.098$), with a positive but statistically insignificant correlation ($p > 0.05$) and an r^2 of 0.011, indicating that PCSK9 levels influence LDL cholesterol in CKD patients by 1.1%. Similar findings have been reported in other studies. For example, the study by Dounousi E et al. in Greece with 92 CKD patients found an average PCSK9 level of 278.1 ng/mL, with no correlation between PCSK9 levels and kidney function, lipid profile parameters, or inflammatory markers.[27]

The study by Rogacev et al. analyzing CKD patients from stage 2 to stage 4 found no correlation between PCSK9 levels and glomerular filtration rate.[30] Similarly, Morena M in France found no statistical significance between PCSK9 levels and GFR ($p = 0.770$) or proteinuria ($p = 0.888$). PCSK9 levels did not significantly differ across CKD stages.[31] However, some studies have investigated genetic and ethnic factors affecting PCSK9 and LDL cholesterol levels. It was found that genetic factors can influence serum PCSK9 and LDL cholesterol levels. The study by Lakoski et al. found that the average PCSK9 level was higher in the Hispanic group (508 ng/mL), the African American group (478 ng/mL), and the European-American group (490 ng/mL). Ethnic differences also affect LDL cholesterol reduction in cases of PCSK9 loss-of-function mutations. Lakoski et al. evaluated the effects of PCSK9 loss-of-function mutations in the African-American group, where there was an average reduction of 40% in LDL cholesterol levels. The European-American group experienced an average reduction of 21% in LDL cholesterol. This study demonstrates that genetics from various ethnic groups affect PCSK9 and serum LDL cholesterol levels.[29]

Furthermore, this study was conducted regardless of the therapy administered. Type 2 diabetes mellitus was found in all samples. Insulin therapy, commonly administered to patients with type 2 diabetes, can influence PCSK9 levels. In mice, insulin can increase liver PCSK9 mRNA. Insulin increases SREBP1 expression in hepatocytes, resulting in higher PCSK9 expression. However, insulin can also activate protein kinase γ, thereby inhibiting Hepatocyte Nuclear Factor 1α (HNF1α), which leads to reduced PCSK9 expression in hepatocytes.[25] Additionally, dyslipidemia therapy, which was an exclusion criterion in this study, only included statins, whereas other anti-lipid medications can affect LDL cholesterol levels. Bile acid sequestrants can lower LDL cholesterol by 15-30%, niacin can reduce LDL cholesterol by 5-25%, fibrates can decrease LDL cholesterol by 5-20%, and ezetimibe can lower LDL cholesterol by 10-18%.[32]

CONCLUSIONS

This study found no significant correlation between Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) levels and Low-Density Lipoprotein (LDL) cholesterol in chronic kidney disease (CKD) patients, though a very weak positive correlation was observed. These results suggest that PCSK9 may have a limited impact on LDL levels in this population. Further research with larger sample sizes and varied lipid therapies is needed to better understand this relationship and the factors influencing it.

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