Lipid Profile in Early and Late Stage among Patients with Nephrotic Syndrome-Related Chronic Kidney Disease in Dr. Hasan Sadikin General Hospital Bandung, Indonesia in 2016–2019

Haya Hanif Mahardika,[1] Ahmedz Widiasta,[2] Viramitha Kusnandi Rusmil[2]

[1]Faculty of Medicine Universitas Padjadjaran, Indonesia, [2]Department of Child Health, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Abstract

Background: Chronic kidney disease (CKD) is a major health problem in children with an increased prevalence globally. CKD is strongly associated with Nephrotic Syndrome (NS) and dyslipidemia, which become a progressive factor of CKD. This study aimed to describe the lipid profile of children with CKD and NS in Dr. Hasan Sadikin General Hospital Bandung, Indonesia.

Methods: An observational-retrospective study was conducted with a cross-sectional design involving 150 medical records of children aged 1–18 years who were diagnosed with CKD with NS. Lipid profile data, including total cholesterol, triglycerides, LDL, and HDL, were collected from 2016–2019 using the total sampling method. Subjects with incomplete lipid profile data were excluded from the study.

Results: Among the fifty-two children that were eligible and fulfilled the inclusion criteria, 88.5% were diagnosed with stage 1 CKD, and 32.7% were aged between 6–11 years and boys were predominant (67.3%). Lipid profile changes were found in the LDL, HDL, and total cholesterol serum levels between CKD stage I and II–V.

Conclusions: Lipid profile of CKD pediatric patients with NS in Dr. Hasan Sadikin General Hospital Bandung in 2016–2019 showed hypertriglyceridemia and hypercholesterolemia. Most subjects were in stage I of CKD and Steroid-Resistant Nephrotic Syndrome, and comparison between stages of CKD and types of nephrotic syndrome is lacking. A prospective analytical study would be more reliable in proofing its significance.

Keywords: Chronic kidney disease, cholesterol, lipid profile, nephrotic syndrome, triglyceride

Introduction

According to the National Kidney Foundation Disease Outcome Quality Initiative (NKF K/DOQI), chronic kidney disease (CKD) is defined as kidney abnormalities whether it is structurally or functionally, present for ≥3 months with significant impact on the health with or without decreased glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 body surface area (BSA).[1–3] CKD is a major health problem in children with an increased prevalence globally. The annual incidence rate is 8%.[4] Based on data from Riset Kesehatan Dasar (RISKESDAS) 2018, the prevalence of CKD among adolescents (≥15 years old) in West Java is 0.48%, of which dyslipidemia is the major risk factor.[5] A research conducted in Dr. Hasan Sadikin General Hospital Bandung in 2016, the number of children's CKD cases was 52.[6]

Nephrotic Syndrome (NS) is commonly found in children. According to the International Study of Kidney Disease in Children (ISKDC), NS is defined as having proteinuria >40 mg/m^2/hour with hypoalbuminemia, swelling, and hyperlipidemia.[7] Globally, its incidence is 2–7 cases/100.000 children. Patients with progressive NS in resistant-steroid type might lead CKD and or end-stage kidney disease (ESKD).[7] Hyperlipidemia is one of the several manifestations of NS and is caused by increased lipoprotein synthesis by the liver and decreased lipoprotein lipase activity.[8] Hypercholesterolemia has been reported in children with NS.[9,10] Dyslipidemia, a known risk factor for atherosclerosis, has become the main focus in clinical research,

Correspondence: Ahmedz Widiasta, dr., Sp.A(K), M.Kes, Department of Child Health, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Jalan Pasteur No. 38, Bandung, Indonesia, E-mail: ahmedzwidiasta@gmail.com

as it is a potentially modifiable risk factor.[10,11] However, the study regarding the lipid profile of pediatric CKD and NS in Dr. Hasan Sadikin General Hospital Bandung is limited. In addition, dyslipidemia, as one of the factors contributing to the progression of pediatric CKD, is often under-treated despite notable advances in its treatment.[12]

This study aimed to describe the lipid profiles in children with CKD and NS in Dr. Hasan Sadikin General Hospital Bandung from 2016 to 2019. This study may suggest a new strategy for treatment plans early as possible. Furthermore, this study may increase clinicians' knowledge and awareness regarding lipid profiles in children with CKD and NS, and might serve as a new basis for future research.

Methods

This study was an observational study with a cross-sectional design. Data on children diagnosed with CKD with NS in Dr. Hasan Sadikin General Hospital Bandung in 2016–2019 were retrieved from Hospital Information System of Hasan Sadikin General Hospital. Furthermore, complete lipid profile laboratory examinations were collected. Inaccessible medical records were excluded from this study. This study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran no. 74/UN6.KEP/EC/2019 and LB.02.01/X.2.2.1/1722/2019.

Data on subjects' characteristics such as age, gender, and laboratory results of lipids were collected. Age was defined as the patient's age at the time of CKD diagnosis. The children's age was based on the National Institute of Child Health and Human Development (NICHD) standard and categorized into infant (<2 years old), toddler (2–5 years old), early childhood (6–11 years old), and adolescent (12–18 years old).[13]

Lipid laboratory results were categorized based on the American Academy of Pediatrics (AAP) 2020.[14,15] Triglyceride (TG) values were categorized differently for 1–9 years and >9–18 years-age group. For 1–9 years-age group, triglycerides value was categorized into acceptable (<75 mg/dL), borderline-high (75–99 mg/dL), and high (≥100 mg/dL), whereas for the >9-18 years-age group, acceptable (<90 mg/dL), borderline-high(90–129 mg/dL); high (≥130 mg/dL). Total cholesterol (C) values were categorized into acceptable (<170 mg/dL), borderline-high (170–199 mg/dL), and high (≥200 mg/dL). The LDL values were categorized into acceptable (<110 mg/dL), borderline-high (110–129 mg/dL), and high (≥130 mg/dL). The HDL values were categorized into low (<40 mg/dL), borderline-high (40–45 mg/dL), and acceptable(>45 mg/dL).[14]

Diagnosis and stages of CKD were based on diagnosis in the medical records. All analyses were performed with Microsoft® Excel2016 dan IBM® SPSS® ver 22. The data were presented as mean and standard deviation.

Results

Of the 150 patients' data collected, only 52 met the inclusion criteria namely children aged 1–18 years , diagnosed with CKD and NS and had their lipid profile examined, including total cholesterol, triglycerides, LDL, and HDL. The lipid profiles in the other subjects were excluded due to their inadequacy lipid profile data. Some subjects only had their cholesterol

Table 1 Characteristics of Children with Chronic Kidney Disease on Stages of Nephrotic Syndrome (n=52)

Characteristics	Stage of NS based CKD	
	STAGE I n(%)	STAGE II–V n(%)
Age group		
<2 years	5(9.6)	0(0)
2–5 years	16(30.8)	1(1.9)
6–11 years	17(32.7)	3(5.7)
12–18 years	8(15.4)	2(3.8)
Gender		
Male	31(59.7)	4(7.6)
Female	15(28.8)	2(3.8)

Note: CKD= chronic kidney disease; NS= nephrotic syndrome

Table 2 Laboratory Results of Lipid Measurement of Children with Chronic Kidney Disease and Nephrotic Syndrome based on Stages (n=52)

	Mean ± SD	Total	Stage I n(%)	Stage II–V n(%)
Triglycerides, 1–9 years of age; N=35	269.88 ± 204.3**			
Acceptable		2 (3.8)	2 (3.8)	0 (0)
Borderline-high		4 (7.7)	3 (5.7)	1 (1.9)
High		29 (55.8)	27 (51.9)	2 (3.8)
Triglycerides, >9–18 years of age; n=17				
Acceptable		2 (3.8)	2 (3.8)	0 (0)
Borderline-high		5 (9.6)	5 (9.6)	0 (0)
High		10 (19.2)	7 (13.5)	3 (5.7)
Total Cholesterol	309.1 ± 175.5			
Acceptable		11 (21.2)	10 (19.2)	1 (1.9)
Borderline-high		9 (17.3)	7 (13.5)	2 (3.8)
High		32 (61.5)	29 (55.8)	3 (5.7)
LDL	223.3 ± 158			
Acceptable		14 (26.9)	13 (25)	1 (1.9)
Borderline-high		6 (11.5)	4 (7.7)	2 (3.8)
High		32(61.5)	29(55.8)	3(5.7)
HDL	48.8 ± 17.3			
Acceptable		29(55.8)	26(50)	3(5.7)
Borderline-high		9(1.3)	8(1.,4)	1(1.9)
Low		14(26.9)	12(23)	2(3.8)

Note: ** both aged groups; results were reported using mean and standard deviation for quantitative variables

or triglyceride tests because of the standards applied by the health system by the hospital before the study was conducted.

The characteristics of children in the age group 6–11 years had the highest number (38.5%), followed by the age group 2–5 years (32.7%). More than half of the subjects were comprised of boys (67.3%) with a mean age of 7.23 ± 4.5 years. Stage I CKD has a higher frequency than stage II–V.

In general, the subjects had high category lipid laboratory measurement results. The majority of subjects were CKD stage I with steroid-resistant nephrotic syndrome (92.3%) as illustrated in Table 2.

Based on laboratory results of lipid measurements, triglyceride values in the two age groups 1–9 and >9–18 years were included in the high category. Interestingly, in the 1–9 years of age group, 61.5% were CKD stage 1, whereas in the >9–18 years it was 26.9%. The high category was also found in other lipid measurement values. Of all subjects at all stages of CKD, 61.5% had high total cholesterol serum and 21.1% were in the acceptable category. The LDL result also showed 61.5% were in the high category. Similar to other lipid measurements, HDL was shown at 55.8%, which was in the acceptable category as shown in Table 2.

Discussions

Hypertriglyceridemia, hypercholesterolemia, or combined dyslipidemia have been found in more than half of the children, whereas most of them were diagnosed with stage 1 CKD and steroid-resistant nephrotic syndrome. Hypertriglyceridemia was found in both groups of 1–9 years old and >9–18 years old, and the majority had stage 1 CKD due to reduced activity of lipoprotein lipase in plasma.[16,17] In contrast, higher triglyceride level in the higher CKD stage were found in adult cases.[6] The discrepancies between child and adult cases were caused by the underlying mechanism. Most CKD in adulst was related to diabetes mellitus, obesity, and hypertension.[6] Hence the change in lipid profile is usually found in the early stage of CKD. In children, most CKD is related to glomerular disease and congenital anomalies. In contrast, the

histologic morphology of vessels and the heart were still normal.[3,6]

The dyslipidemic condition reflects an altered metabolism of lipoprotein. The suggested mechanisms are dyslipidemic condition, which might be due to decreased activity of lecithin cholesterol acyltransferase (LCAT), hepatic lipase due to proteinuria, and lipoprotein lipase. These reduced enzyme activities affects lipoprotein metabolism and have its mechanisms. Reduced activity of LCAT, possibly due to its deprivation in plasma, results in a depletion of cholesterol ester esterification from cholesterol to be carried by HDL and impair the HDL maturation, leading subsequently to sustained triglycerides enrichment of HDL and explaining hypertriglyceridemia condition. This mechanism is compound with the depletion of LCAT.[18,19] It is also reported that decreased lipoprotein lipase is responsible for LDL elevation due to impaired cholesterol transfer into peripheral tissue.[16]

In the patient with CKD only, reduced HDL level in serum is commonly found.[20] While in this study, a significant high HDL, low LDL, and total cholesterol serum levels were found in the early CKD stage, consistent with a study on a nephrotic patient in which normal to reduced HDL.[8,16] Nephrotic range proteinuria affects the clearance of HDL in circulation by decreasing hepatic lipase activity in liver. Increased Cholesteryl Ester Transfer Protein (CETP), reduced hepatic expression of Scavenger Receptor-B 1 (SR-B1), and LCAT loss are the mechanism suggested that causing HDL metabolism dysfunction results in cholesterol ester-poor and triglyceride-rich lipoprotein; thus normal-to-low HDL found in serum. The majority of the children are not at stage 1 CKD and proteinuria. These account for acceptable HDL serum. In the early stages of CKD, commonly found an acceptable or decreased HDL serum level condition while reduced HDL is generally present in patients with advanced CKD and ESRD.[21]

The limitation of this study is that not all pediatric CKD patients with NS have lipid profile analysis, thereby reducing the number of potential subjects to be included in the sample. Furthermore, the lipid profile of patients with CKD and NS should be tested as early as possible after the diagnosis is established. The data do not represent all stages in CKD or NS, because most of the subjects were CKD stage I and steroid-resistant NS resulting in a lack of comparison between stages of CKD and types of NS. More advanced statistical analysis would be more reliable in proving the significance of this study. As a consideration, the condition of worsening dyslipidemia might be complicated by cardiovascular disease, as it is known as a risk factor for atherosclerosis. Thus, children with CKD should be screened for dyslipidemia.[22,23]

In conclusion, dyslipidemic children mostly found in the early stage of CKD. This study only provides a temporary picture of lipid profile in a short period which prevents the collection of more comprehensive data on patients size and numbers. A future prospective study with a longer period is needed to monitor the lipid profile in relation to the progression of NS and CKD.

References

1. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63(5):713–35.
2. Levin A, Stevens PE., Bilous RW, Coresh J, De Fransisco ALM, De Jong PE, et al. Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1–150.
3. Becherucci F, Roperto RM, Materassi M, Romagnani P. Chronic kidney disease in children. Clin Kidney J. 2016;9(4):583-91.
4. Halle MP, Lapsap CT, Barla E, Fouda H, Djantio H, Moudze BK, Akazong CA, Priso EB. Epidemiology and outcomes of children with renal failure in the pediatric ward of a tertiary hospital in Cameroon. BMC Pediatr. 2017;17(1):202.
5. Badan Penelitian dan Pengembangan Kesehatan. RISKESDAS 2018. Jakarta: Badan Penelitian dan Pengembangan Kesehatan;2018.
6. Widiasta A, Pardede SO, Rachmadi D. Correlation between LDL, HDL, total cholesterol , and triglyceride with the degree of chronic kidney disease in children. Am J Clin Med Res. 2017;5(1): 1–5.
7. Hussain N, Zello JA, Vasilevska-Ristovska J, Banh TM, Patel VP, Patel P, et al. The rationale and design of Insight into Nephrotic Syndrome: Investigating Genes, Health and Therapeutics (INSIGHT): a prospective cohort study of childhood

nephrotic syndrome. BMC Nephrol. 2013;14:25.
8. Pandey JC, Prasad CK. Lipid profile abnormalities in nephrotic syndrome. Asian J Biomed Pharm Sci. 2016;6(54): 17–19.
9. Dnyanesh D, Dnyanesh S, Shenoy V. A study of serum lipids in nephrotic syndrome in children. IOSR J Dent Med Sci 2014;13(3): 1–6.
10. Krishnaswamy D, Indumati V, Satishkumar D, Vijay V, Shekanawar Maharudra, Maligi Amareshwara, et al. Serum proteins, initial and follow-up lipid profile in children with nephrotic syndrome. Int J Appl Biol Pharm Technol. 2011;2(3): 59–64.
11. Said S, Hernandez GT. The link between chronic kidney disease and cardiovascular disease. J Nephropathol. 2014;3(3):99–104.
12. Wilson AC, Schneider MF, Cox C, Greenbaum LA, Saland J, White CT, et al. Prevalence and correlates of multiple cardiovascular risk factors in children with chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(12):2759–65.
13. National Institute of Child Health and Human Development US Department of Health and Human Services. The NICHD study of early child care and youth development: - findings for children up to age 4 1/2 years [Internet]. Washington, DC: US Government Printing Office; 2006. [Cited 2021 August 28]. Available from: https://www.nichd.nih.gov/publications/product/20
14. Stewart J, McCallin T, Martinez J, Chacko S, Yusuf S. Hyperlipidemia. Pediatr Rev. 2020;41(8):393–402.
15. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128 Suppl 5(Suppl 5):S213–56.
16. Vaziri ND. Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences. Kidney Int. 2016;90(1):41–52.
17. Chan DT, Dogra GK, Irish AB, Ooi EM, Barrett PH, Chan DC, et al. Chronic kidney disease delays VLDL-apoB-100 particle catabolism: potential role of apolipoprotein C-III. J Lipid Res. 2009;50(12):2524–31.
18. Blaton V. Dyslipidemia at chronic renal failure. EJIFCC. 2009;20(1):59–66.
19. Ooi EM, Chan DT, Watts GF, Chan DC, Ng TW, Dogra GK, et al. Plasma apolipoprotein C-III metabolism in patients with chronic kidney disease. J Lipid Res. 2011;52(4):794–800.
20. Saland JM, Pierce CB, Mitsnefes MM, Flynn JT, Goebel J, Kupferman JC, et al. Dyslipidemia in children with chronic kidney disease. Kidney Int. 2010;78(11):1154–63.
21. Vaziri ND. HDL abnormalities in nephrotic syndrome and chronic kidney disease. Nat Rev Nephrol. 2016;12(1):37–47.
22. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. J Am Soc Nephrol. 2012;23(4):578–85.
23. Tian J, Niu L, An X. Cardiovascular risks in chronic kidney disease pediatric patients. Exp Ther Med. 2017;14(5):4615–9.