Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.62, No.6(2022). p.404-10; DOI: https://doi.org/10.14238/pi62.6.2022.404-10

Original Article

Comparison of lipid profile values in pediatric patients with cyanotic and acyanotic congenital heart disease

Fifi Febria Ningsih, Hafaz Zakky Abdillah, Selvi Nafianti

Abstract

Background Incidence of congenital heart disease (CHD) is about 0.8% of every child born. This heart defect is associated with dyslipidemia in children. Lipid profiles examination in patients with CHD can be used to determine risk factors for atherosclerosis.

Objective To examine differences in lipid profiles in children with cyanotic and acyanotic CHD.

Methods This was a cross-sectional study on 60 pediatric CHD patients at Haji Adam Malik Hospital, Medan, North Sumatera, from December 2020 to March 2021. Subjects were included by consecutive sampling. Data of patient's age, gender, weight, height, complete blood count, blood glucose, and lipid profiles were recorded. Unpaired T-test analysis and Mann-Whitney test were then performed to analyze variables in cyanotic and acyanotic CHD patients.

Results Of a total of 60 CHD children, 26 subjects had a diagnosis of cyanotic CHD and 34 subjects had a diagnosis of acyanotic CHD. The most common cause of cyanotic CHD was tetralogy of Fallot (76.9%), while the most common cause of acyanotic CHD were ventricular septal defect and patent ductus arteriosus (32.4% each). Analysis of lipid profiles on both groups revealed that low density lipoprotein (LDL) was significantly lower in the cyanotic group than in the acyanotic group ($P<0.05$). However, other lipid profile values, were not significantly different between groups. In addition, there was no significant difference in incidence of dyslipidemia between cyanotic and acyanotic CHD.

Conclusion Low density lipoprotein is significantly lower in the cyanotic CHD group than in the acyanotic CHD group. But there are no significant differences in the other lipid profiles measurement and incidence of dyslipidemia between groups. **[Paediatr Indones. 2022;62:404-10; DOI: https://doi.org/10.14238/pi62.6.2022.404-10**].

Keywords: *congenital heart disease; dyslipidemia; cyanotic*

Congenital heart disease (CHD) are abnormalities in the structure or function of the heart circulation from birth that occur due to disruption or failure of development of the heart structure in the early stages of fetal development.[1] Clinical manifestations depend on the severity of the disease, ranging from asymptomatic to the presence of symptoms of heart failure in neonates.[2] Congenital heart disease is divided into two main categories, namely, cyanotic and acyanotic.[1]

More than a quarter of children with CHD are overweight.[3] There are two leading causes of overweight in children with CHD, physical activity restriction and high-calorie diet. Infants with CHD were given a high-calorie diet to compensate increased caloric needs for surgical repair but some parents continue to give their children high-calorie diet even after the surgery and resolvement of the heart defect.[4]

Dyslipidemia is a lipid metabolism disorder characterized by an increase or decrease in plasma

From the Department of Child Health, Universitas Sumatera Utara Medical School, Medan, South Sumatera, Indonesia.

Corresponding author: Fifi Febria Ningsih. Jalan Bunga Lau No. 17, Medan 20136, North Sumatera, Indonesia. Telp. +62 8127523773; Email: fifi_febria@yahoo.com.

Submitted August 20, 2021. Accepted December 5, 2022.

lipids.[5] It plays an important role in heart disease. This CHD has been associated with dyslipidemia in children.[6] On other hand, both uncorrected and corrected CHD in adults have a low incidence of coronary heart disease.[7] Furthermore, cyanotic CHD patient has a lower risk of coronary heart disease.[8]

Further study is needed to develop recommendations for comparing lipid profiles in CHD patients. As such, we aimed to compare lipid profiles in pediatric patients with cyanotic or acyanotic CHD.

Methods

This was a cross-sectional study to assess differences in lipid profiles between children with cyanotic and acyanotic CHD. The study was conducted at Haji Adam Malik Hospital, Medan, North Sumatera, from December 2020 to April 2021. The target population was CHD patients aged 1 month - 18 years and had not undergone heart correction. Patients with chronic liver disease, chronic kidney disease, or myeloproliferative disease were excluded from the study.

Lipid profiles examinations were done after patients had fasted for 10 to 12 hours. Dyslipidemia was a lipid metabolism disorder characterized by an increase or decrease in the lipid fraction in plasma, namely, an increase in total cholesterol levels (≥200mg/dL), LDL cholesterol (>130 mg/dL), triglyceride levels (≥100 mg/dL), and/or a decrease in high density lipoprotein (HDL) levels (≤ 40 mg/dL), according to *The National Cholesterol Education Program* (NCEP) cut-off value.[9]

Nutritional status was assessed based on WHO 2006 weight-for-height charts in children under 5 years old and *CDC 2000* charts in children above 5 years of age. *WHO* and *CDC* classified nutritional status into obesity, overweight, normal, wasting, and stunting. In this study, we grouped nutritional status in to three categories: (1) normal if weight-for-height is between -2 to +2 SD in *WHO* chart and BMI between 5th to 85th percentile in *CDC 2000,* (2) wasting if weight-for-height is between -3 to -2 SD in *WHO* chart and BMI below 5th percentile in *CDC* 2000, and (3) stunting if weight-for-height is under -3 SD in *WHO* chart and height-for-age below 5th percentile in *CDC 2000*.[10]

Data analysis was conducted with SPSS version 26.0. Multivariate analysis was used to determine the distribution of subject's characteristics. Numerical data were presented in mean and standard deviation and categorical data were presented in frequency and percentage. Unpaired T-test was used for normally distributed data and the Mann-Whitney test was used for non-normally distributed data. Chi-square test was used for categorical data and the Fischer's exact test was used when the Chi-square test conditions were not met. P values <0.05 were considered to be statistically significant, with 95% confidence intervals (CI). This study was approved by the Health Research Ethics Committee, Universitas Sumatera Utara, Medical Faculty.

Results

A total of 60 pediatric patients diagnosed with CHD who visited the outpatient or inpatient units of Haji Adam Malik Hospital, Medan, North Sumatera, were included. The 60 patients included 26 children with cyanotic CHD and 34 children with acyanotic CHD. The mean age of children in the cyanotic CHD group was 5.55 years and in the acyanotic CHD group was 3.88 years. In the cyanotic CHD group, most subjects were stunted (12/26), while in the acyanotic CHD group, most subjects had normal nutritional status (16/34). The characteristics of subjects are presented in **Table 1**.

As shown on **Table 2**, the most common cause of cyanotic CHD was tetralogy of Fallot (20/26). Meanwhile, the most common type of acyanotic CHD was VSD and PDA (11/34) in each group. **Table 3** shows the lipid profiles in the two study groups. Mann-Whitney test revealed no significant differences in mean cholesterol and triglycerides levels, but there was a significant higher LDL level in acyanotic CHD group. Independent T-test revealed no significant difference in mean HDL level between the two groups. **Table 4** shows the differences in lipid profiles of cyanotic and acyanotic groups, by categorizing each of them into high and normal groups. Fischer's exact test revealed no significant difference in the percentages of subjects with high total cholesterol or high LDL levels between the two groups. Chi-square test revealed no significant differences in the percentages of subjects

Table 1. Characteristics of subjects

Characteristics	Cyanotic CHD (n=26)	Acyanotic CHD (n=34)
Gender, n(%)		
Male	15	14
Female	11	20
Mean age (SD), years	5.55 (4.28)	3.88 (4.29)
Age by group, n		
<5 years	13	26
5 – <10 years	8	3
10 – < 15 years	4	5
15–18 years	1	0
Nutritional status, n		
Normal	7	16
Wasting	7	10
Stunting	12	8

Table 2. Type of CHD in cyanotic and acyanotic groups.

Cyanotic CHD (n=26)		Acyanotic CHD (n=34)	
ToF	20	ASD	5
TGA-IVS	1	VSD	11
DORV	5	PDA	11
		ASD + PDA	3
		ASD + VSD	1
		ASD + PDA + VSD	1
		VSD + PDA	1
		Pulmonary stenosis	1

ToF=tetralogy of Fallot; TGA-IVS=transposition of great arteries-intact ventricular septum; DORV=double outlet right ventricle; ASD=atrial septal defect; VSD=ventricular septal defect; PDA=patent ductus arteriosus.

Table 3. Lipid profiles in cyanotic and acyanotic groups.

Lipid profiles	Cyanotic CHD (n = 26)	Acyanotic CHD (n = 34)	P value
Total cholesterol, mg/dL			0.052[a]
Mean (SD)	122.04 (33.56)	136.15 (34.86)	
Median (range)	116.5 (76-210)	133.5 (58-210)	
Triglycerides, mg/dL			0.359[a]
Mean (SD)	125.58 (56.69)	115.12 (60.54)	
Median (range)	116.5 (49-222)	97.5 (45-256)	
HDL, mg/dL			0.301[b]
Mean (SD)	33.23 (12.14)	36.29 (10.56)	
Median (range)	34 (12-61)	35.5 (10-62)	
LDL, mg/dL			0.023[a]
Mean (SD)	80.65 (32.75)	96.56 (31.74)	
Median (range)	75 (29-157)	95.5 (22-202)	

[a]Mann-Whitney; [b]independent T-test

with high triglyceride or low HDL levels between the two groups.

Of our 60 CHD subjects, there were 55 children with dyslipidemia based on their lipid profiles. **Table 5** shows results of independent variables and dyslipidemia analysis.

Table 4. Dyslipidemia in congenital heart disease

Lipid profiles	Cyanotic CHD (n=26)	Acyanotic CHD (n=34)	Prevalence ratio (95%CI)	P value
Total cholesterol, n			1.167 (0.418 to 3.254)	1.000[a]
High	2	2		
Normal	24	32		
Triglycerides, n			1.091 (0.610 to 1.952)	0.768[b]
High	14	17		
Normal	12	17		
HDL, n			0.932 (0.482 to 1.803)	0.832[b]
Normal	7	10		
Low	19	24		
LDL, n			0.750 (0.233 to 2.417)	0.689[a]
High	2	4		
Normal	24	30		

[a]Fischer's exact; [b]Chi-square

Table 5. Analysis of factors potentially associated with dyslipidemia in children with CHD

Variables	Dyslipidemia		PR (95% CI)	P value
	Yes (n=55)	No (n=5)		
Gender, n (%)			1.109 (0.952 to 1.290)	0.355[a]
Male	28	1		
Female	27	4		
Mean age (SD), years	4.70 (4.38)	3.48 (4.03)		0.718[b]
< 5 years	35	4 (10.3)		
5-10 years	11	0		
10 - < 15 years	8	1		
15-18 years	1	0		
Nutritional status, n (%)			1.088 (0.912 to 1.297)	0.362[a]
Wasting and stunting	35	2		
Normal	20	3		
Type of CHD, n (%)			1.012 (0.869 to 1.179)	1.000[a]
Cyanotic	24	2		
Acyanotic	31	3		

[a]Fischer's exact; [b]Mann-Whitney

Discussion

In general, the number of acyanotic CHD patients is three to four times greater than that of cyanotic. Despite this lower prevalence, cyanotic CHD causes higher morbidity and mortality than acyanotic CHD.1 In our study of 60 CHD subjects, there were 26 subjects with a diagnosis of cyanotic CHD and 34 subjects with a diagnosis of acyanotic CHD.

The incidence of CHD varies among populations, according to studies from different countries, incidence of CHD is ranging from 4 to 50 per 1,000 live births. These mixed results are related to differences in inclusion criteria, environmental and genetic factors, lack of appropriate health care systems and follow-up, lack of available detection modalities, limited diagnostic techniques, and undocumented national data.[11] In our study, ToF was the most common cause of cyanotic CHD (76.9%), which was in accordance with a previous study that reported a 68.2% of ToF;[12] while VSD and PDA (32.4% each) were the most common cause of acyanotic CHD, which was similar with a study reporting 30.3% VSD, 24.5% ASD, and 13.9% PDA.[13] However, another study reported that PDA was the most common acyanotic CHD, followed by VSD and ASD with prevalences of 44%, 25%, and 25%, respectively.[14]

Patients with cyanotic CHD usually have

more severe growth retardation than patients with acyanotic CHD.[15] The cardiac basal metabolic rate (BMR) in children with cyanotic CHD is higher than in children with acyanotic CHD.[16] Many factors influence the nutritional status of infants and children with CHD, including type of CHD, nutrient input (low energy intake, malabsorption), energy requirements (hypermetabolism), dietary components, age at surgery, and prenatal factors.[17,18] In our study, stunted was found in 46.2% of cyanotic CHD subjects and 23.5% of the acyanotic group. Chi-square analysis revealed no significant difference between groups. A previous study reported malnutrition is higher in cyanotic CHD patients (63.6%) compared to acyanotic CHD patients (30.6%).[12]

Barbiero *et al.*[19] reported malnutrition is higher in acyanotic CHD (27.7%) group than in cyanotic CHD group (23.3%). This is in contrast with our study that shown malnutrition is higher in the cyanotic group (46.2%) than acyanotic group (23.5%). Physical activity and diet misperceptions by parents cause their children to be overweight. Parents often restrict their children's physical activity and increase their calorie intake as they perceive their child as "sick" and vulnerable even though the defect is small or has been surgically corrected.[4]

The prevalence of obesity has increased rapidly in recent decades and is now recognized as an independent risk factor for cardiovascular diseases and diabetes. Obesity is often associated with other cardiovascular risk factors, such as atherogenic dyslipidemia. Although most of the clinical burden of cardiovascular disease occurs in adulthood, these risk factors can develop during childhood and adolescence. In fact, there is now clear evidence that atherosclerosis begins in childhood. To reduce cardiovascular mortality, we need to turn our attention to preventing and correcting these risk factors before adulthood when the atherosclerotic process may have progressed too far to be reversible with therapy. Although CHD is associated with high mortality, only 0.4% of deaths from cardiovascular disease are attributable to CHD in the United States.[19] However, a study reported that CHD did not increase the risk of dyslipidemia in children.[20]

The diagnosis of dyslipidemia is made by measuring blood lipids, lipoproteins, or apolipoprotein factors. If there is an abnormality on the measurement, a diagnosis of specific dyslipidemia is made, such as elevated total cholesterol, LDL-C, apo B, non-HDL-C, and triglycerides (TGs) or a lower-than-normal level of HDL-C.[18]

In our study mean LDL level was significantly higher in the acyanotic group than in the cyanotic group (P=0.023). There was no difference in the incidence of dyslipidemia in the two groups. To the best of our knowledge, no studies have specifically compared lipid profiles between cyanotic and acyanotic CHD patients. Moreover, a study found no difference in the prevalence of coronary intimal hyperplasia in cyanotic vs. acyanotic CHD patients.[21] The TGF-β1 immunostaining was negative for all controls and similar between cyanotic and acyanotic CHD, but was significantly greater in corrected vs. uncorrected CHD.[22] It is suspected that hypoxia-ischemia induces vascular injury that occurs before or during cardiac surgery (such as hemodynamic instability, cardiac arrest, or coronary manipulation). They identified five variables that contributed to the low incidence of atherosclerosis in cyanotic patients, namely, hypocholesterolemia, hypoxemia, upregulation of nitric oxide (NO), hyperbilirubinemia, and low platelet count.[8]

Fyfe *et al.*[23] reported that hypocholesterolemia occurred in 58% of patients with cyanotic CHD who did not undergo surgery and in 52% of patients who had corrective surgery. Only 11% of cyanotic CHD patients with preoperative hypocholesterolemia had postoperative elevated cholesterol. Hypocholesterolemia primarily reflects a reduction in LDL cholesterol with a lower reduction in VLDL and HDL cholesterol.[23] The major contribution of apo-B-containing lipoproteins to total cholesterol implies underproduction or overuse of VLDL, HDL, or LDL, as the mechanism responsible for low total cholesterol levels. Underproduction occurs in malnutrition with mutations in the apo-B protein leading to decreased VLDL production and with mutations in the microsomal triglyceride transfer protein that reduce cholesterol absorption in the gut.[24] A previous study found that proliferating cells in polycythemia vera and myeloid metaplasia display abnormal cholesterol metabolism and derepression, as regards the negative feedback regulation is usually mediated by the LDL receptor.[25] Increased in vivo LDL catabolism in hypocholesterolemic subjects with

myeloproliferative disease supports this hypothesis.

In conclusion, LDL level is significantly lower in cyanotic CHD than in acyanotic CHD. But there is no significant difference in the incidence of dyslipidemia between cyanotic and acyanotic CHD patients.

Conflict of interest

None declared.

Funding acknowledgement

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Sastroasmoro S, Madiyono B. Epidemiologi dan etiologi penyakit jantung bawaan. In: Sastroasmoro S, Madiyono B, editors. Buku ajar kardiologi anak. Jakarta: IDAI; 1994. p. 165-190.
2. Djer MM, Madiyono B. Tata laksana penyakit jantung bawaan. Sari Pediatri. 2000;2:155-62. DOI: https://dx.doi.org/1014238/sp2.3.2000.155-62.
3. Shustak RJ, McGuire SB, October TW, Phoon CKL, Chun AJL. Prevalence of obesity among patients with congenital and acquired and heart disease. Pediatr Cardiol. 2012;33:8-14. DOI: https://dx.doi.org/10.1007/s00246-011-0049-y.
4. Hansen SR, Dørup I. Energy and nutrient intakes in congenital heart disease. Acta Paediatr. 1993;82:166-72. DOI: https://doi.org/10.1111/j.1651-2227.1993.tb12632.x.
5. Fakhrzadeh H, Tabatabaei-Malazy OT. Dyslipidemia and cardiovascular disease. 2012. [cited 2022 OCT 10]. p.303-20. Available from: https://cdn.intechopen.com/pdfs/27503/InTech-Dyslipidemia_and_cardiovascular_disease.pdf.
6. Chikanna S, Upadhyay A, Aneja GK. Lipid profile in high risk children aged 2-10 years. Indian Pediatr. 2010;47:630-1. PMID: 20683118.
7. Giamberti A, Lo Rito M, Conforti E, Varrica A, Carminati M, Frigiola A, *et al.* Acquired coronary artery disease in adult patients with congenital heart disease: a true or a false problem? J Cardiovasc Med. 2017;18:605-9. DOI: https://doi.org/10.2459/JCM.0000000000000495.
8. Perloff JK. The coronary circulation in cyanotic congenital heart disease. Int J Cardiol. 2004;97:79-86. DOI: https://doi.org/10.1016/j.ijcard.2004.08.018.
9. Wilson DP, McNeal C, Blackett P. Pediatric dyslipidemia: recommendations for clinical management. South Med J. 2015;108:7-14. DOI: https://doi.org/10.14423/SMJ.0000000000000219.
10. Dawson-Hahn EE, Pak-Gorstein S, Hoopes AJ, Matheson J. Comparison of the nutritional status of overseas refugee children with low income children in Washington State. PLoS One. 2016;11:e0147854. DOI: https://doi.org/10.1371/journal.pone.0147854.
11. Hoffman JIE. Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002:39:1890-900. DOI: https://doi.org/10.1016/S0735-1097(02) 01886-7.
12. Wulandari AP, Ontoseno T, Umiastuti P. Hubungan status gizi anak usia 2-5 tahun dengan kelainan jantung bawaan biru di RSUD Dr Soetomo Surabaya. Sari Pediatri. 2018;20:65-9.
13. Liu Y, Chen S, Zühlke L, Babu-Narayan SV, Black GC, Choy MK, Li N, Keavney BD. Global prevalence of congenital heart disease in school-age children: a meta-analysis and systematic review. BMC Cardiovasc Disord. 2020;20:488. DOI: https://doi.org/10.1186/s12872-020-01781-x.
14. Khasawneh W, Hakim F, Abu Ras O, Hejazi Y, Abu-Aqoulah A. Incidence and Patterns of Congenital Heart Disease Among Jordanian Infants, a Cohort Study From a University Tertiary Center. Front Pediatr. 2020 May 5;8:219. DOI: https://doi.org/10.3389/fped.2020.00219.
15. Modi P, Suleiman MS, Reeves BC, Pawade A, Parry AJ, Angelini GD, Caputo M. Basal metabolic state of hearts of patients with congenital heart disease: the effects of cyanosis, age, and pathology. Ann Thorac Surg. 2004;78:1710-6. DOI: https://doi.org/ 10.1016/j.athoracsur.2004.05.010.
16. Wisnuwardhana M. Manfaat pemberian diet tambahan terhadap pertumbuhan pada anak dengan penyakit jantung bawaan asianotik. Semarang: Universitas Diponegoro; 2006. [cited 2022 Oct 10]. Available from: http://eprints.undip.ac.id/18130/.
17. Forchielli ML, McColl R, Walker WA, Lo C. Children with congenital heart disease: a nutrition challenge. Nutr Rev. 1994;52:348-53. DOI: https://doi.org/10.1111/j.1753-4887.1994.tb01359.x.
18. Park KM. Dyslipidemia and other cardiovascular risk factors. In: Park MK, editor. Park's pediatric cardiology for practitioners. 6th ed. Philadelphia: Mosby Elsevier; 2008. p. 852-900.
19. Barbiero SM, Sica CD, Schuh DS, Cesa CC, Petcowicz RO, Pellanda LC. Overweight and obesity in children with congenital heart disease: combination of risks for the future?. BMC Pediatr. 2014;14;271. DOI: https://doi.

org/10.1186/1471-2431-14-271.

20. Fuenmayor C, Redondo ACC, Shiraishi KS, Souza R, Elias PF, Jatene IB. Prevalence of dyslipidemia in children with congenital heart disease. Arq Bras Cardiol. 2013;101:273-6. DOI: https://doi.org/10.5935/abc.20130174.
21. Justino H, Khairy P. Congenital heart disease and coronary atherosclerosis: a looming concern?. Canadian Journal of Cardiology. 2013;29:757-58. DOI: https://doi.org/10.1161/CIRCULATIONAHA.118.037064.
22. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, *et al*. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459-72. DOI: https://doi.org/10.1093/eurheartj/ehx144.
23. Fyfe A, Perloff JK, Niwa K, Child JS, Miner PD. Cyanotic congenital heart disease and coronary artery atherogenesis. Am J Cardiol. 2005;96:283-90. DOI: https://doi.org/10.1016/j.amjcard.2005.03.060.
24. Welty FK, Ordovas J, Schaefer EJ, Wilson PW, Young SG. Identification and molecular analysis of two apoB gene mutations causing low plasma cholesterol levels. Circulation. 1995;92:2036-40. DOI: https://doi.org/10.1161/01.cir.92.8.2036. PMID: 7554178.
25. Gilbert HS, Ginsberg H, Fagerstrom R, Brown WV. Characterization of hypocholesterolemia in myeloproliferative disease. Relation to disease manifestations and activity. Am J Med. 1981;71:595-602. DOI: https://doi.org/10.1016/0002-9343(81)90212-6.