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ORIGINAL ARTICLE

HDL-Cholesterol in Children and Adolescents with Congenital Heart Disease

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Abstract

Background: Children and adolescents with congenital heart disease may be more likely to develop atherogenic cardiovascular diseases in adulthood. Therefore, the early identification of risk factors and intervention in childhood may be crucial for a good quality of life and longevity.

Objectives: To describe the distribution of high-density lipoprotein-cholesterol (HDL-c) levels and its association with socioeconomic, clinical and cardiovascular risk factors in children and adolescents with congenital heart disease.

Methods: Cross-sectional study with children and adolescents aged between 5 and 18 years, with congenital heart disease. Socioeconomic, clinical and cardiovascular risk factors were evaluated. HDL-c concentrations were evaluated by the direct method and categorized as desirable (>45 mg/dL), borderline (40-45 mg/dL) and low (<40 mg/dL). We also assessed the "undesirable" levels, consisting of the sum of "borderline" and "low" values for comparative purposes. The multivariate logistic regression analysis was used to evaluate the factor associated with undesirable HDL-c levels. A $p<0.05$ value was adopted as statistically significant.

Results: Mean HDL-c was 51.2 mg/dL (SD 12.6), with a prevalence of 33.2% of undesirable HDL-c. In the multivariate analysis, C-reactive protein levels ≥ 3mg/dL (OR 3.26; 95% CI 1.32-8.04), age ≥ 10 years old (OR: 2.11; 95% CI 1.12-3.99) and undesirable levels of triglycerides (OR 2.21; 95% CI 1.13-4.75) were associated with undesirable HDL-c.

Conclusion: In this sample of children and adolescents with congenital heart disease, almost one third presented low or borderline HDL-c levels. Age ≥10 years, C-reactive protein and triglycerides were associated with undesirable HDL-c levels. These factors should be considered in the prevention of cerebrovascular diseases in adulthood in this population.

Keywords: Child; Adolescent; Atherosclerosis; Heart Defects, Congenital/genetics; Dyslipidemia; Cholesterol; HDL-Cholesterol/genetics; Risk Factors.

Introduction

Advances in pediatric cardiology have allowed the early diagnosis and better therapeutic options for children with congenital heart disease. Consequently, these patients live longer, with an increase in the number of adults with this condition, who are subject to complications not only of the primary disease, but also of atherosclerotic cardiovascular diseases (CVD).[1,2]

Clinical manifestations of CVD are caused by a progressive atherosclerotic process, with a long preclinical phase that may last decades.[3] According to the multicentric study Pathobiological Determinants of Atherosclerosis in Youth (PDAY), in which a risk scores for subclinical atherosclerosis in inviduals aged 15 to 34 years was constructed, risk factors for atherosclerosis in young individuals are comparable to those in older adults and the elderly.[4]

Dyslipidemia is considered one of the main predictors of CVD.[5] There is robust evidence that increased high-density lipoprotein cholesterol (HDL-c) levels reduce the relative risk of CVD, mainly due to their cardiovascular protective effects, such as the reverse cholesterol transport, the stabilizing effect on the endothelium and

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the antioxidant activity.[5,6] Besides, important negative associations between HDL-c and inflammatory markers – surgery, obesity, repeated infections and C-reactive protein – have been demonstrated.[7]

It is estimated that at least one fourth of patients with congenital heart disease are physically inactive, either because of clinical limitations or excessive care by their caregivers.[8,9] In addition, these patients are more susceptible to inflammation, due to complications of interventions, or due to acute infections, mainly with pulmonary involvement.[10,11]

Since atherosclerosis is often asymptomatic in children, the risks of this condition may be underestimated by health professionals. Thus, the identification of the risk factors for atherosclerosis is fundamental, and prospective studies have suggested that the earlier the intervention, the better the prevention of atherothrombotic events.[12,13]

This study aimed to describe the prevalence of HDL-c levels and to assess their correlation with socioeconomic and clinical characteristics, and cardiovascular risk factors in children and adolescents with congenital heart disease.

Methods

This was a cross-sectional study. Individuals aged 5 to 18 years with congenital heart disease, in the late postoperative period (>6 months) after interventional catheterization or cardiac surgery, were considered eligible for the study. Patients attending routine clinical visits in two pediatric cardiology outpatient clinics in the state of Santa Catarina, Brazil, between August and December 2016 were recruited.

Exclusion criteria included secondary diagnosis of malignant neoplasm, chromosomal abnormalities, familial hypercholesterolemia, diabetes mellitus, hypothyroidism, other inflammatory chronic diseases and acute inflammatory diseases in the last 15 days.

Data collection

Data collection was carried out between January and July 2017; participants underwent an interview, a physical examination, and laboratory tests on the same day. A multiprofessional team was responsible for data collection and was composed of a pediatric cardiologist, a nutritionist, a physical educator, and a medical student. A structured instrument, previously standardized and calibrated among the investigators, was constructed for data collection.

Sociodemographic characteristics

The following sociodemographic variables were evaluated: age (years), sex, self-reported skin color, per capita income (<1 minimum wage and ≥ 1 minimum wage, based on the minimum wage in Brazil in February 2017) and maternal schooling (< 10 years or ≥ 10 years).

Clinical characteristics

Clinical variables included: type of congenital heart disease (cyanotic or acyanotic), interventional procedures (interventional catheterization or surgery), use of medications (yes/no; beta-blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, diuretics, antiplatelet and anticoagulant agents), number of hospitalizations for community-acquired infections (≤ 2 times or > 2 times) and family history of early coronary artery disease (yes/no; in men < 45 years of age or women < 55 years of age).

Cardiovascular risk factors

Venous blood samples were collected after 10-12 hours of fasting. Total cholesterol (TC) and triglycerides levels were determined by the enzymatic method (Dimension®; Siemens) and HDL-c levels were measured by the direct *in vitro* method.[14] Concentrations of LDL-c were calculated using the Friedewald formula since no patients showed triglyceride levels higher than 400 mg/dL. Non-HDL cholesterol (non-HDL-c) levels were calculated by subtracting HDL-c from TC. Lipid parameters were classified according to the Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[15] HDL-c levels were categorized as (1) desirable (>45 mg/dL); (2) borderline (40-45 mg/dL) and (3) low (<40 mg/dL). Also, "undesirable" HDL-c levels were adopted for comparative analysis and defined as the sum of borderline HDL-c with low HDL-c levels.

Fasting glucose concentrations were determined by the enzymatic colorimetric method and classified according to the American Diabetes Association (ADA) criteria.[16] Lipid and glucose parameters classified as moderate and high were grouped for comparative purposes.

High-sensitivity C-reactive protein (hs-CRP) levels were determined by highly sensitive immunonephelometry[17] and classified as low risk (<1 mg/L), moderate risk (1-3 mg/L) or high risk (≥3 mg/L),[18] and also as low/moderate risk (<3 mg/L) and high risk (≥3 mg/L) for comparative purposes.

Blood pressure measurements were performed using a calibrated aneroid sphygmomanometer as described in "The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents".[19] Hypertension was defined as systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) ≥95th percentile for sex, age and height.

Regarding the anthropometric parameters, body weight and height were measured for calculation of body mass index (BMI) and classification of nutritional status as follow: BMI-for-age, classified according to the z-scores for children and adolescents using the World Health Organization standards[20,21] (overweight/obesity: z-score > +1); waist circumference (cm), measured and classified according to age- and sex-specific cut off points proposed by Fernandez et al.;[22] values above the 75th percentile were considered excess abdominal adiposity.[22] Physical activity was assessed using the Physical Activity Questionnaire for Children (PAQ-C),[23] and participants were classified as physically inactive or active. We also assessed screen time (abnormal if ≥ 2 hours/day),[24] passive or active smoking (yes/no, reported by their caregivers).

Statistical analysis

For sampling, an unknown prevalence of the outcome was considered – undesirable HDL-c (50%) for a total of 430 children and adolescents with congenital heart disease seen at the hospitals of the study. The margin of sampling error was plus or minus 3.0 percentage points; and the type 1 and 2 errors of 5% and 20%, respectively were adopted, resulting in 204 individuals. Another 15% were added for possible dropouts or rejections, yielding 235 individuals.

Normality of data distribution was tested using the Kolmogorov-Smirnov test, histogram and variability coefficient. For descriptive analysis, relative and absolute frequencies, 95% confidence interval (95% CI), means and standard deviation were calculated. The independent t-test was used for comparison of HDL-c levels by sociodemographic characateristics. To evaluate the association between undesirable HDL-c levels and cardiovascular risk factors, bivariate analysis was performed using the chi-square test or Fisher's exact test, depending on group size. To determine associations of socioeconomic and clinical characteristics, and cardiovascular risk factors with undesirable HDL-c levels, multivariate logistic regression analysis was performed using the forward method. All variables of interest were dichotomized for the logistic regression analysis; those with p<0.20 associations in the chi-square test and considered important for the theoretical model[7,25,26] were tested. Variables with multicollinearity were excluded from the multivariate analysis (r=0.5). Multivariate logistic regression models were simultaneously adjusted for sex, income, type of congenital heart disease, type of intervention, number of hospitalizations for community-acquireed infections, use of medications, waist circumference and physical activity. Results were expressed as Odds ratio (OR) and respective 95% CIs.

All analyses were performed using the SPSS software version 23 (SPSS, Inc., Chicago, IL, USA), and a p<0.05 was considered statistically significant.

Ethical aspects

An informed consent form was signed by participants' parents or guardians. The study was approved by the local ethics committee (approval number 1.672.255/2016) and was in accordance with the 466/2012 resolution and other resolutions of the Brazilian National Ethics Committee.

Results

A total of 232 individuals were included; most were older than 10 years (52.2%), female (52.6%) and white (87.1%). Most patients had acyanotic congenital heart disease (65.9%), with ventricular septal defect as the most common (15.9%). All patients had undergone a cardiac invervention at least six months before, 82.3% a cardiac surgery and 17.7% therapeutic catheterization. Nineteen percent of patients had more than two hospitalizations for community-acquired infections.

Table 1 describes the distribution of HDL-c levels by sociodemographic and clinical characteristics. Patients ≥ 10 years of age showed significantly lower concentrations of HDL-c compared with patients younger than 10 years. Patients with acyanotic congenital heart disease showed significantly higher levels of HDL-c as compared with patients with cyanotic congenital heart disease.

Mean HDL-c was 51.2 mg/dL (SD 12.6); 23.3% of patients showed borderline levels and 9.9% showed low HDL-c levels; 33.2% of children and adolescents with congenital heart disease showed undesirable HDL-c levels. The following cardiovascular risk factors were found to be associated with low HDL-c levels – being insufficiently active, screen time longer than two hours per day, passive smoking, abdominal obesity, positive

Table 1 – Distribution of high-density lipoprotein-cholesterol concentrations according to sociodemographic and clinical characteristics of children and adolescents with congenital heart disease (n=232)

Variables		N	Mean	95% CI	p*
Sociodemographic characteristics					
Age	< 10 years ≥ 10 years	111 121	53.5 49.1	45.0-62.0 39.0-57.0	0.01
Sex	Female Male	122 110	52.0 50.3	43.8-59.0 40.0-61.3	0.31
Skin color	White Others	202 30	51.1 51.7	42.0-59.0 40.7-63.3	0.81
Per capita income	<1 minimum wage ≥ 1 minimum wage	157 75	50.5 52.6	41.0-58.0 45.0-63.0	0.24
Maternal education†	< 10 years ≥ 10 years	99 131	50.8 51.7	42.0-60.0 42.0-61.0	0.60
Clinical characteristics					
Type of congenital heart disease	Cyanotic Acyanotic	79 153	48.8 52.4	41.0-57.0 43.0-63.0	0.04
Type of cardiac interventional procedure	Catheterization Surgery	41 191	53.2 50.8	46.0-62.0 41.0-59.0	0.25
Use of medications	No Yes	175 57	51.7 49.8	39.5-59.5 43.0-60.0	0.32
Number of hospitalizations for community-acquired infections	≤ 2 >2	187 45	51.3 50.84	42.0-59.0 39.0-61.5	0.85
Family history of early coronary artery disease ‡	Negative Positive	177 51	51.3 50.8	41.0-61.5 43.0-57.0	0.80

95% CI = 95% confidence interval
** unpaired Student's t-test*
†=2 missing data
‡= 4 missing

family history of cardiovascular disease, borderline glucose levels, and increased hs-PCR. The distribution of cardiovascular risk factors by HDL-c classification are described in Table 2.

Table 3 shows the results of the bivariate analysis among socioeconomic, clinical and cardiovascular risk factors and undesirable HDL-c levels. Age and hs-PCR showed significant associations with undesirable HDL-c levels.

In the multivariate logistic regression analysis – adjusted for sex, income, type of congenital heart disease, type of procedure, number of hospitalizations for community-acquired infections, use of medications, waist circumference, C-reactive protein ≥3 mg/L, age ≥ 10 years and triglycerides ≥75/≥90 mg/dL (according to age) were associated with HDL-c levels, as shown in Table 4.

Discussion

This cross-sectional study showed an important prevalence of dyslipidemia in children and adolescents with congenital heart disease, mainly attributed to low HDL-c levels (9.9% of patients with low HDL-c levels, mean 51.2 mg/dL, 95% CI 38.6-63.8 mg/dL). These findings contrast with two previous studies with children with congenital heart disease conducted in 2013 – one of them was a cross sectional study[27] carried out in São Paulo State/Brazil with 52 children with congenital heart disease, in which no significant changes in HDL-c levels were observed in this group by the authors; another study was a case-control study conducted in Iran, which showed that the group with congenital heart disease (case

Table 2 – Cardiovascular risk factors according to high-density lipoprotein cholesterol (HDL-c) classification in children and adolescents with congenital heart disease (n=232)

Cardiovascular risk factors *	Reference	Total n (%)	HDL-c classification		
			Desirable n (%) 155 (66.8)	Borderline n (%) 54 (23.3)	Low n (%) 23 (9.9)
Total cholesterol	Desirable (<170 mg/dL)	184 (79.3)	114 (73.5)	48 (88.9)	22 (95.7)
	Borderline (170-199 mg/dL)	43 (18.5)	37 (23.9)	5 (9.3)	1 (4.3)
	High (≥ 200 mg/dL)	5 (2.2)	4 (2.6)	1 (1.9)	0 (0)
LDL-Cholesterol	Desirable (<110 mg/dL)	185 (79.7)	124 (80)	44 (81.5)	17 (73.9)
	Borderline (110-129 mg/dL)	31 (13.4)	22 (14.2)	5 (9.3)	4 (17.4)
	High (>130 mg/dL)	16 (6.9)	9 (5.8)	5 (9.3)	2 (8.7)
Non-HDL-Cholesterol	Desirable (<120 mg/dL)	174 (75)	119 (76.8)	40 (74.1)	15 (65.2)
	Borderline (120-144 mg/dL)	36 (15.5)	23 (14.8)	8 (14.8)	5 (21.7)
	High (≥145 mg/dL)	22 (9.5)	13 (8.4)	6 (11.1)	3 (13.0)
Triglycerides	Desirable*	179 (77.2)	122 (78.7)	40 (74.1)	17 (73.9)
	Borderline*	38 (16.4)	22 (14.2)	13 (24.1)	3 (13)
	High*	15 (6.5)	11 (7.1)	1 (1.9)	3 (13)
Fasting glucose	Desirable (<100 mg/dL)	201 (86.6)	137 (88.4)	45 (83.3)	19 (82.6)
	Borderline (>100 and < 126 mg/dL)	31 (13.4)	18 (11.6)	9 (16.7)	4 (17.4)
hs-CRP†	Low risk (<1 mg/L)	82 (35.7)	69 (44.5)	11 (20.4)	2 (8.7)
	Moderate risk (1 - 3 mg/L)	119 (51.7)	73 (47.1)	32 (59.3)	14 (60.9)
	High risk (≥ 3 mg/L)	29 (12.6)	13 (8.4)	10 (18.5)	6 (26.1)
Systolic blood presusure	Desirable (≤ 90th percentile)	227 (97.8)	151 (97.4)	53 (98.1)	23 (100)
	Borderline (>90th percentile)	3 (1.3)	2 (1.3)	1 (1.9)	0 (0)
	High (≥ 95th percentile)	2 (0.9)	2 (1.3)	0 (0)	0 (0)
Diastolic blood pressure	Desirable (≤ 90th percentile)	227 (97.8)	153 (98.7)	52 (96.3)	22 (95.7)
	Borderline (>90th percentile)	3 (1.3)	1 (0.6)	1 (1.9)	1 (4.3)
	High (≥ 95th percentile)	2 (0.9)	1 (0.6)	1 (1.9)	0 (0)
Physical activity ‡	Active (Score 1 - 3)	10 (4.4)	6 (3.9)	2 (3.7)	2 (8.7)
	Insufficiently active (Score 4 - 5)	217 (95.6)	144 (92.9)	52 (96.3)	21 (91.3)
Screen time	< 2 hours/day	109 (47)	71 (45.8)	26 (48.1)	12 (52.2)
	≥ 2 hours/day	123 (53)	84 (54.2)	28 (51.9)	11 (47.8)
Passive or active smoking §	No	172 (75.1)	114 (73.5)	41 (75.9)	17 (73.9)
	Yes	57 (24.9)	39 (25.2)	12 (22.2)	6 (26.1)
BMI/age	Normal (< +1 z-score)	188 (81.0)	125 (80.6)	47 (87)	16 (69.6)
	Overweight / obesity (≥+1 z-score)	44 (19.1)	30 (19.4)	7 (13)	7 (30.4)
Waist circumference //	Desirable (<75 percentile)	170 (73.3)	113 (72.9)	44 (81.5)	13 (56.5)
	Abdominal obesity (≥75 percentile)	57 (24.6)	38 (24.5)	9 (16.7)	10 (43.5)

LDL: low-density lipoprotein; BMI/age: body mass index-for-age; hs-CRP: high-sensitivity C-reactive protein.
*%: relative frequency; n: absolute frequency; *, †, ‡, §, //, ¶, #, **, ††, *: according to the Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents,[15] and the American Diabetes Association[16]*
†: two missing data
‡: five missing data
§: three missing data
//: five missing data

Table 3 – Bivariate analysis of the association of undesirable high-density lipoprotein-cholesterol (HDL-c) levels (<40mg/dL) with sociodemographic, clinical and cardiovascular risk factors in children and adolescents with congenital heart disease (n=232)

Variable	Risk factor	chi-square	p
Sociodemographic characteristics			
Age	≥ 10 years	4.79	**0.03**
Sex	Male	3.29	0.07
Skin color	Non-white	0.19	0.66
Per capita income	<1 minimum wage/person	2.13	0.15
Maternal education	<10 years	0.60	0.44
Clinical characteristics	Acyanotic	2.89	0.09
Type of heart disease	Cardiac surgery	2.84	0.09
Type of procedure	Yes	2.71	0.10
Use of medications	>2 times	1.17	0.28
Number of hospitalizations for community-acquired infections			
Family history of early coronary heart disease	Positive	0.01	0.94
Cardiovascular risk factors			
Total cholesterol	≥170 mg/dL	0.40	0.53
LDL-cholesterol	≥110 mg/dL	0.02	0.89
Non-HDL-cholesterol	≥120 mg/dL	0.78	0.38
Triglycerides	≥75/≥90 mg/dL*	0.64	0.42
Fasting glucose	≥100 mg/dL	0.001	0.98
hs-CRP	≥3 mg/L	7.68	**0.01**
Systolic blood pressure	Hipertension	1.00†	1.00
Diastolic blood pressure	Hipertension	0.26†	1.00
Physical activity	Inactive	0.17†	0.74
Screen time	≥2 hours/day	0.26	0.61
Passive smoking	Yes	0.09	0.77
BMI/age	≥ +1 z-escore	0.05	0.83
Waist circumference	≥ 75th percentile	0.001	0.98

BMI/age: body mass index-for-age; hs-CRP: high-sensitivity C-reactive protein
IMC/I: Índice de Massa Corporal para Idade; PCRus: Proteína C Reativa Ultrassensível
**: Triglyceride levels were classified according to the following recommendations – children <9 years of age: desirable <75 mg/dL and borderline ≥ 75 mg/L; and children 10-19 years of age: desirable <90 mg/dL and borderline/high ≥ 90 mg/dL*
†: Fisher's exact test

group) had significantly higher mean HDL-c levels than the group without the disease (control group).[28] Further studies are needed to clarify these differences.

In the present study, mean HDL-c level was 51.2 mg/dL (SD 12.6). In an apparently healthy group of 1,009 children and adolescents in the city of Florianopolis,[29] Brazil, in 2009, mean HDL-c level was 53.4 mg/dL (95% CI 52.6-54.2 mg/dL), but the prevalence of undesirable HDL-c (<45 mg/dL) was lower (23%) than in our study (33.25). This difference may be explained by the higher exposure of children and adolescents with congenital heart disease to inflammatory stimuli – therapeutic

Table 4 – Factors associated with undesirable high-density lipoprotein cholesterol (HDL-c) (<40 mg/dL) in children and adolescents with congenital heart disease (n=232)

	Undesirable HDL-c (<40 mg/dL)					
	Unadjusted			Adjusted *		
Risk factors						
hs-CRP						
<3.0 mg/L	1			1		
≥3.0 mg/L	2.96	1.34-6.54	**0.01**	3.26	1.32-8.04	**0.01**
Age						
<10 years	1			1		
≥10 years	1.86	1.06-3.25	**0.03**	2.11	1.12-3.99	**0.02**
Triglycerides						
<75 /<90 mg/dL†	1			1		
≥75 /≥90 mg/dL†	1.30	0.69-2.46	0.42	2.21	1.13-4.75	**0.04**

hs-CRP: high sensitivity C-reactive protein
**Adjusted for: sex, income, type of congenital heart disease, number of hospitalizations for community-acquired infections, use of medications, waist circumference, and physical activity*
†: Triglyceride levels were classified according to the following recommendations – children <9 years of age: desirable <75 mg/dL and borderline ≥ 75 mg/L; children 10-19 years of age: desirable <90 mg/dL and borderline/high ≥ 90 mg/dL

procedures, infections – that demand the production of several pro-inflammatory mediators at expenses of HDL-c synthesis[30] – in addition to greater restrictions on exercise and diet, with is supported by the literature.[25,31]

In addition, we found that patients with cyanotic congenital heart disease had lower HDL-c levels in comparison with patients with acyanotic congenital heart disease. So far, no study has evaluated HDL-c levels and type of heart disease. In a prospective study[11] with patients aged 8-19 years old with a history of severe congenital heart disease, a higher probability of low HDL-c (<40 mg/dL) was found in these patients (RR 1.79 [1.36-2.35]) compared with healthy children in the same age range, but no comparative analysis was made between cyanotic and acyanotic heart diseases.

The Brazilian Study of Cardiovascular Risks in Adolescents (ERICA, *Estudo de Risco Cardiovascular em Adolescentes*) determined the prevalence of cardiovascular risk factors in adolescents in the country. The study revealed a high prevalence of dyslipidemia, mainly of low HDL-c, followed by increased TC levels. The prevalence of low HDL-c was significantly higher in the North and Northeast regions, where the Human Development Index is the lowest, a similar trend to that found in developing countries.[32] In the last years, a historical trend of improvement in HDL-c levels has been observed in developed countries, where the environmental stress seems to be more controlled. This trend contrasts with that found in developing countries, but with no direct relationship between low HDL-c and the prevalence of obesity or metabolic syndrome in these populations, which could also explain this behavior. Another study, the National Health and Nutrition Examination Survey (NHANES), showed a decrease in the prevalence of undesirable lipid levels in the American pediatric population, including low HDL-c, from 17.9% (1999-2000) to 12.8% (2011-2012).[33,34] In contrast, in Taiwan, there was an increase in low HDL-c levels from 6.5% in 1996 to 11.6% in 2006.[35] In Forianopolis, an increase in the prevalence of low HDL-c was seen in children, from 5% in 2001 to 23% in 2009.[29,36] It is of note that high HDL-c levels in children and adolescents observed in developed countries like Spain and Japan ha been associated with relatively low mortality for CVD in developed countries.[37,38]

These differences in HDL-c found in different geographic locations may be due to several factors, including genetic and dietetic factors, as physical activity,

and environmental stress, facilitating the exposure of children to inflammatory stimuli. Better public policies are usually implemented in developed countries, including awareness-raising programs for healthy diet, exercise, and obesity control. Studies[29,32] have suggested that heredity may have a strong impact on HDL distribution in Brazil, due to its great ethnic diversity.

Also, studies[33,34] have shown an inverse relationship between HDL-c levels and age.[33,34] Studies of the second half of the 20th century, like the Bogalusa Heart Study,[3] demonstrated, in a sample of children, that increase in age was associated with a decrease in HDL-c levels.[3] This is in accordance with our results, that showed an association between age ≥ 10 years and undesirable HDL-c levels. It is possible that the contemporary lifestyle is associated with a greater exposure to inflammatory stimuli, since early childhood, exemplified by repeated infections of pre-school children attending day care centers. However, further studies on environmental and clinical factors of patients with congenital heart disease are needed, to develop strategies for controlling the variables responsible for the reduction of HDL-c levels in the studied patients.

In addition, data highlighting the obesity pandemic have reported a high prevalence of elevated triglyceride levels in children in both developed and developing countries.[39] One of the most accepted definitions of metabolic syndrome in children is the co-occurrence of insulin resistance, arterial hypertension, dyslipidemia (increased triglyceride and decreased HDL-c levels) and abdominal obesity.[40] Obesity *per se* causes a metabolic disturbance, which combined with an elevation of triglycerides, culminates in a persistent inflammatory state and decreased HDL-c levels.[41]

Similarly to the study by Giuliano et al.,[29] we showed an inverse relationship between low HDL-c and high triglyceride levels. This pattern of dyslipidemia has been described as the most common in contemporary children.[39] In another study, the authors evaluated data from the National Health and Nutrition Examination Survey (NHANES), of children aged 5-19 years, and confirmed that the increase in age is accompanied by an increase in the prevalence of hypertriglyceridemia, especially in overweight and obese individuals.[33,34] This may be explained by the high proportion of children who are insufficiently active and have poor dietary habits (e.g. a trans fatty acid-rich diet), which is in fact a world trend. These individuals become more exposed to such inflammatory stimuli over time.

Our sample showed increased levels of hs-CRP, which may be a result of surgical stress, increased vulnerability to repeated infections, and elevation in triglyceride concentrations, associated with a sedentary lifestyle and high intake of trans-fatty acids. Similarly to previous studies,[25,29] increased hs-CRP was associated with a higher risk of undesirable HDL-c levels, which may be explained by a deviation in the metabolic pathway during the synthesis of acute phase proteins, which leads to suppression of hepatic lipoprotein production, particularly HDL.[25,29]

Increasing evidence has shown an association of low family income and low maternal education with low HDL-c levels, probably related to a subclinical inflammatory status, demonstrated by elevations in hs-CRP. These social determinants of health are related to the inflammatory process that accelerates atherosclerosis progression. On the other hand, it is known that established atherosclerosis *per se* – presence of complex plaques, fibrosis and calcification – is associated with low hs-CRP, leading to a vicious circle.[11,42,43]

This study has some limitations that should be considered. The cross-sectional design of the study precludes inferences regarding the causes of low HDL-c levels, and the absence of a control group does not allow more detailed comparisons. Also, there are other cofounding factors that were not evaluated in the present study, including assessment of sleep, place of residence (rural and urban), and genetic factors.

This is the first Brazilian study to describe the distribution of HDL-c concentrations in a representative sample of patients with congenital heart disease, and to demonstrate the relationship of HDL-c levels with socioeconomic, clinical, and cardiovascular risk factors. The investigation of HDL-c in patients with congenital heart disease is important to determine the risk of atherosclerotic disease and to elucidate whether the underlying disease (combined with the exposure to inflammatory stimuli of therapies or their clinical conditions) would put these patients at high risk for CVD at adulthood. Therefore, understanding the role of each cardiovascular risk factor is crucial in the management of patients with congenital heart disease.

Conclusion

In the present study on children and adolescents with congenital heart disease, almost one third of patients

showed borderline or low levels of HDL-c, which was associated with age, and triglycerides and hs-CRP levels. These findings should be considered in preventive programs for CVD (particularly atherosclerosis and its compications) in this population, aimed at changing lifestyle for improvement of metabolic and inflammatory profiles, and responses to inflammatory triggers inherent to their clinical condition. We suggest further multicentric studies with a prospective, longitudinal design, to test the prospective associations among HDL-c concentrations and atherosclerosis outcomes in children and adolescents with congenital heart disease.

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Author contributions

Conception and design of the research: Cardoso SM, Honicky M, Moreno YMF, Lima LRA, Back IC; acquisition of data: Pacheco MA, Cardoso SM, Honicky M, Marcos CS, Back IC; analysis and interpretation of the data, critical revision of the manuscript for intellectual content and statistical analysis: Pacheco MA, Cardoso SM, Honicky M, Moreno YMF, Lima LRA, Back IC; writing of the manuscript: Pacheco MA, Cardoso SM, Honicky M, Back IC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Comitê de Ética em Pesquisa de Seres Humanos do Hospital Infantil Joana de Gusmão under the protocol number 1.672.255/2016 e 1.877.783/2016. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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