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ORIGINAL ARTICLE

Prevalence of Coronary Artery Disease Risk Factors and Metabolic Syndrome in Children with Heart Disease

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Abstract Children with acquired and congenital heart disease (CHD) are increasingly surviving to adulthood. Our aim was to determine the prevalence of coronary artery disease (CAD) risk factors in children at known risk for early CAD or with severe CHD. We recruited children (8–19 years) at risk for early CAD—Kawasaki disease (KD, $N = 36$) and coarctation (69) or severe CHD: > 1 cardiopulmonary bypass surgery (60), single ventricle (15), prosthetic valves (13). Anthropometric measurements, blood pressure, and fasting lipid data were compared with summaries from National Health and Nutrition Examination Survey (NHANES) publications (1999–2012). Relative risk (RR) ratios were calculated based on age classification and pooled to obtain overall RR. Of 174 subjects, 106 were male (61%) and 138 (79%) had CHD. Compared to NHANES data, hypertension and low HDL were higher in the study cohort [RR 11.7 (CI 6.34–21.6), $p < 0.001$; and 1.79 (CI 1.36–2.35). $p < 0.001$] and obesity and elevated total cholesterol were lower [RR 0.59 (CI 0.37–0.96), $p = 0.03$; and 0.42 (CI 0.19–0.95), $p = 0.04$]. Elevated non-HDL was similar between groups. Age category had similar RR for all CAD risk factors. Eight subjects had metabolic syndrome. Risk factors were similar between KD versus CHD subgroups. Both coarctation and non-coarctation subjects had increased RR for hypertension. Hypertension is the most common risk factor for children at risk of early CAD and severe CHD. Metabolic syndrome is rare. These patients should be screened and treated for hypertension and current recommendations for universal lipid screening are adequate for follow-up.

Keywords Congenital heart disease · Acquired heart disease · Kawasaki disease · Dyslipidemia · Hypertension · Pediatrics · Coronary artery disease

Abbreviations

AAP	American Academy of Pediatrics
BMI	Body mass index
CAD	Coronary artery disease
CHD	Congenital heart disease
HDL	High density lipoprotein
KD	Kawasaki disease
LDL	Low density lipoprotein
NHANES	National Health and Nutrition Examination Survey
RR	Relative risk

Introduction

The atherosclerotic process that leads to coronary artery disease (CAD) is known to begin in childhood and progress throughout adulthood [1–3]. CAD risk factors accelerate the atherosclerotic plaque progression and include many heritable and behavioral causes including the metabolic syndrome. The rapidly increasing number of adults with congenital heart disease (CHD) has raised concerns regarding the effect of concomitant CHD and CAD [4–7]. Children with heart disease, whether acquired, as in Kawasaki disease (KD), or congenital (CHD) have been

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identified as a group at risk for premature CAD [1, 8, 9]. However, there have been few studies evaluating the effect of CHD on the accumulation of multiple known CAD risk factors in children with heart disease.

Children with acquired and CHD may be at increased risk for premature CAD for several reasons: abnormal coronary artery anatomy, inflammation and scarring of the coronary arteries from surgical manipulation or the underlying disease process, cyanosis and reperfusion injuries during surgery, turbulent blood flow and altered hemodynamics from underlying anatomic abnormalities, associated genetic syndromes, ventricular hypertrophy or dilation, and systemic hypertension [3]. CHD includes a heterogeneous group of conditions and there are few data to identify those at highest risk for CAD. Despite this, some investigations have reported an association of Kawasaki disease (KD) and coarctation with early CAD [10–12].

We aimed to determine the prevalence of CAD risk factors including the metabolic syndrome in children and adolescents with acquired and CHD. We included those that may be at higher risk for early CAD (KD and repaired coarctation) and those with severe CHD (defined as > 1 cardiopulmonary bypass surgery, single ventricle physiology, or prosthetic valves).

Methods

This prospective, cross-sectional study was approved by the Institutional Review Board at the University of Utah and the Privacy Board of Primary Children's Hospital. Children aged 8–19 years with a history of KD or severe CHD were prospectively enrolled between October 2011 and November 2014. Severe CHD was defined as children with either a history of repaired coarctation or > 1 cardiopulmonary bypass surgery, single ventricle physiology, or a prosthetic valve. Patients with residual coarctation (resting arm-leg gradient > 10 mmHg) were excluded from the study.

Clinical data were obtained at the time of enrollment and included patient's smoking history and history of patient or first degree family member with a known diagnosis of hypertension, hyperlipidemia, or diabetes. The family history was considered positive if either biological parent or grandparents had a history of early CAD (< 55 years of age) or hyperlipidemia (medical treatment or total cholesterol > 240 mg/dl). Height, weight, and waist circumference were obtained. Two upper extremity blood pressure measurements were obtained by trained personnel using an appropriately sized cuff at least 5 min apart in a sitting position and results were averaged. A lipid panel, blood glucose, and high sensitivity CRP were obtained after ≥ 12 h of fasting. Abnormal clinical or laboratory results were communicated to the patients and, with their permission, to the patient's primary care provider. Abnormal values were based on the current literature [1, 13–16].

Metabolic syndrome was defined as meeting 3 of 5 criteria determined by the National Heart, Lung, and Blood Institute (NHLBI) and American Academy of Pediatrics (AAP) [2, 17]: abdominal obesity (waist circumference $\geq$ 95th percentile), hypertension (systolic blood pressure $\geq$ 95th percentile), low HDL (≤ 40 mg/dl), elevated triglycerides (pre-pubertal patients ≥ 100 mg/dl, pubertal patients ≥ 130 mg/dl), and hyperglycemia (fasting glucose ≥ 100 mg/dl).

Statistical Analysis

Patient demographics, including anthropometric measurements were summarized using mean and standard deviation (SD) and counts (%). The study cohort was sub-divided into groups based on age: 8–11 years (pre-pubertal) and 12–19 years (pubertal). For each CAD risk factor, the number and percentage of patients above the normative threshold value were reported.

Systolic blood pressure, fasting lipid levels, and BMI of the study cohort were compared with the general population using values obtained from the National Health and Nutrition Examination Survey (NHANES) publications (1999–2012) [18–20]. The age category of the study cohort (pre-pubertal vs. pubertal) was matched to the corresponding age cut-offs within each NHANES manuscript. Relative risk (RR) ratios were calculated within each of the age groups (pre-pubertal and pubertal) and pooled using the Cochran-Mantel–Haenszel method to obtain an estimate of the overall relative risk for the study cohort versus the NHANES data [21]. A fixed effects meta-analytic approach was appropriate as heterogeneity was low between age groups as evaluated by a heterogeneity test.

Due to the heterogeneity of the study population and the differing pathophysiologies of KD versus CHD, a subgroup analysis was performed to evaluate the relative risk ratios for systolic blood pressure, fasting lipids, and BMI between KD and CHD subjects. In addition, due to the known association between coarctation and hypertension a second analysis comparing systolic blood pressure in subjects with repaired coarctation versus NHANES data and between subjects without coarctation versus NHANES data was performed. Demographic summaries were performed with SAS v. 9 software and meta-analytic pooling was performed using the RevMan 5.3 software. All tests were two-tailed and statistical significance was evaluated at the 0.05 level.

Results

Of the 174 subjects enrolled, 106 (61%) were male, and nearly 80% of subjects had CHD with half of the CHD subjects having repaired coarctation (Table 1). Personal history risk factors were rare with only three subjects reporting smoking and 1 reporting type 1 diabetes. In contrast, positive family histories were common with premature CAD and/or hypercholesterolemia in 122 (70%). Mean weight, height, and BMI for the entire cohort were above the 50th percentile. The mean waist circumference was below the 50th percentile in both pre-pubertal and pubertal subjects (Table 2).

Hypertension was the most prevalent risk factor, affecting 29 (17%) subjects. Glucose levels were elevated in 8 (5%) subjects, three of these subjects met the diagnostic cutoff for diabetes (including the one patient with a previous diagnosis of type 1 diabetes). Few subjects were above the reference threshold values for cholesterol levels (Table 3).

Body mass index, systolic blood pressure, and lipid levels were compared to the NHANES data (Table 3 and Fig. 1). Overall, children in the heart disease cohort had a lower proportion of obesity (Fig. 1a). There was no significant difference in non-HDL levels. (Figure 1b). In contrast, the proportion of children with hypertension (Fig. 1c) and low HDL (Fig. 1d) was higher in subjects with heart disease compared to NHANES data.

There were no significant differences for any risk factor in the subgroup analysis of CHD versus acquired heart disease (KD) subjects. As expected, the proportion of subjects with hypertension was higher in the repaired coarctation group compared with NHANES data (overall RR 17.5, 95% CI 9.16–33.44, $p < 0.001$). The proportion of subjects with hypertension was also higher in the subjects without coarctation compared to NHANES (overall RR 8.20, 95% CI 3.88–17.32, $p < 0.001$).

Discussion

Children with KD and CHD have a mixed picture of additional CAD risk factors. Hypertension was the most common risk factor in this cohort consistent with findings in adults with CHD and coronary artery disease [7]. Hypertension has been well documented in certain conditions within the study cohort. This is particularly true of children and adults after repair of coarctation of the aorta even in the absence of residual obstruction [22–24]. In the current era, it is thought that earlier diagnosis and repair of coarctation may decrease the long-term risk of systemic hypertension. However, recent studies have shown that following early coarctation repair, blood pressure may normalize for a time in childhood, but abnormal endothelial function and impaired arterial reactivity may lead to systemic hypertension by adolescence and middle-age [23]. Our study demonstrates that hypertension is more prevalent in children with repaired coarctation during adolescents. A similar prevalence of other CAD risk factors between the coarctation group and the NHANES group may suggest

Table 1 Demographics, medical, and family history

	Pre-pubertal $N = 27$ n (%)	Pubertal $N = 147$ n (%)	Total $N = 174$ n (%)
Male	21 (78)	85 (58)	106 (61)
Kawasaki disease	2 (7)	34 (23)	36 (21)
Congenital heart disease*	25 (92)	113 (77)	138 (79)
Coarctation	11 (41)	58 (39)	69 (40)
> 1 Cardiac surgery	12 (44)	48 (33)	60 (34)
Single ventricle	3 (11)	12 (8)	15 (9)
Prosthetic cardiac valve	1 (4)	12 (8)	13 (7)
Clinical history			
Smoking	0 (0)	3 (2)	3 (2)
Diabetes	0 (0)	1 (1)	1 (1)
Hypercholesterolemia	0 (0)	1 (1)	1 (1)
Hypertension	0 (0)	14 (10)	14 (8)
Positive family history*			
Early coronary artery disease	7 (26)	53 (36)	60 (34)
Hypercholesterolemia	16 (59)	91 (62)	107 (61)
Metabolic syndrome	0 (0)	8 (5)	8 (5)

*Subjects may have > 1 enrollment criteria

Table 2 Anthropometric measurements

	Pre-pubertal Mean percentile ± SD	Pubertal Mean percentile ± SD	Total Mean percentile ± SD
Weight	42 ± 33	59 ± 30	54 ± 31
Height	53 ± 33	53 ± 29	53 ± 30
BMI	39 ± 35	59 ± 30	54 ± 31
Waist circ.	36 ± 30	47 ± 30	44 ± 30

Waist circ waist circumference

Table 3 Prevalence of coronary artery disease risk factors

Risk factor (threshold)	Pre-pubertal ($N = 27$) *n* (%)	NHANES RR (95% CI)	Pubertal ($N = 144$) *n* (%)	NHANES RR (95% CI)	Total ($N = 171$) *n* (%)	NHANES RR (95% CI)	*p* value
BMI (≥ 95th percentile)	2 (7)	0.57 (0.14–2.2)	17 (12)	0.6 (0.36–1.0)	19 (11)	0.59 (0.37–0.96)	0.03
Systolic BP (≥ 95th percentile)	3 (11)	5.91 (1.84–18.96)	26 (18)	13.46 (6.63–27.31)	29 (17)	11.7 (6.34–21.6)	< 0.001
Total cholesterol (≥ 200 mg/dl)	1 (7)	0.53 (0.08–3.68)	5 (3)	0.4 (0.16–0.98)	6 (4)	0.42 (0.19–0.95)	0.04
Non-HDL cholesterol (≥ 145 mg/dl)	1 (4)	0.54 (0.08–3.75)	8 (5)	0.57 (0.28–1.15)	9 (5)	0.56 (0.29–1.10)	0.09
HDL cholesterol (≤ 40 mg/dl)	7 (26)	2.48 (1.27–4.85)	43 (30)	1.7 (1.26–2.29)	50 (29)	1.79 (1.36–2.35)	< 0.001
Waist circumference (≥ 90th percentile)	2 (7)	NA	13 (9)	NA	15 (9)	NA	NA
Triglycerides *pre-pubertal* (≥ 100 mg/dl) *Pubertal* (≥ 130 mg/dl)	5 (19)	NA	15 (10)	NA	NA	NA	NA
Glucose (≥ 100 mg/dl)	$N = 27$ 2 (7)	NA	$N = 143$ 6 (4)	NA	$N = 170$ 8 (5)	NA	NA
High sensitivity CRP (≥ 3 mg/l)	$N = 26$ 3 (1)	NA	$N = 142$ 5 (4)	NA	$N = 168$ 8 (5)	NA	NA

BMI body mass index, *BP* blood pressure, *CRP* C-reactive protein, *HDL* high density lipoprotein, *NA* not applicable, *RR* relative risk

that cardiovascular morbidity and mortality in this group is primarily driven by systemic hypertension rather than early onset of other CAD risk factors.

Due to the known association between coarctation and hypertension, we performed a subgroup analysis comparing coarctation and non-coarctation patients with NHANES data. As expected, the relative risk for elevated blood pressure was greatest in subjects with repaired coarctation. However, it was also elevated for those without coarctation. As in coarctation, altered vascular hemodynamics and endothelial dysfunction may contribute to hypertension in our non-coarctation patients [25]. These vascular changes have also been shown in patients with KD; including those with no history of coronary artery aneurysms [10, 11]. These findings underscore the importance of following the current recommendations of evaluating blood pressure in children with KD and CHD, specifically repaired coarctation of the aorta, at each encounter and at least on a yearly basis [26].

Current cholesterol screening recommendations in children suggest universal screening at ages 9–11 years [2]. Our study does not demonstrate a need to screen children with at-risk heart conditions or severe CHD more aggressively. Compared with the reference population, there was no difference in the proportion of subjects with elevated non-HDL cholesterol. This finding is particularly important in patients with KD as there have been concerns regarding abnormal lipid profiles [27]. However, unlike previous notions about higher incidence of lipid abnormalities in the KD cohort, our findings are consistent with previous studies that evaluated lipid profiles in KD patients and did not find a difference [28].

The clinical importance of lower HDL cholesterol in our cohort is not clear. Historically, low HDL levels were a well-established risk factor for CAD [29, 30]. More

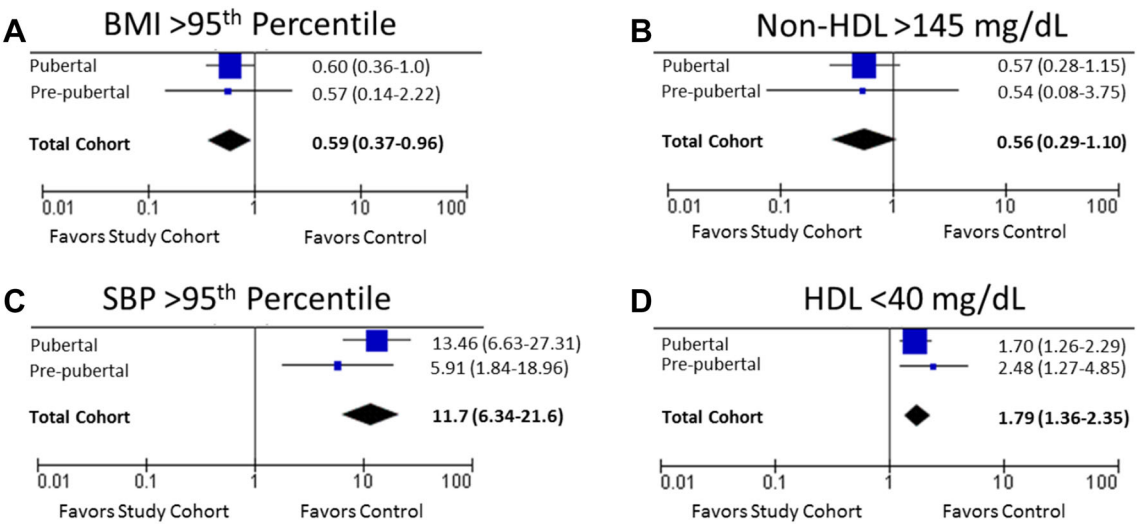

Fig. 1 Relative risk of coronary artery disease risk factor in children with high-risk heart disease compared to NHANES

recently, however, the importance of HDL levels as a modifiable risk factor for coronary artery disease has become controversial, as these levels may be more related to socioeconomic, lifestyle, and other medical conditions [31]. Low HDL levels have been associated with sedentary behaviors and improve with exercise [32]. Exercise limitations inherent to the patient's condition and those imposed by physicians or parents have been implicated as a cause for obesity in the CHD population and may be related to our finding of higher proportion of low HDL [33]. The proportion of children with elevated total cholesterol was lower in our cohort compared to NHANES data. Total cholesterol is no longer a primary therapeutic target and has been replaced in recent guidelines by LDL and non-HDL cholesterol measurements [17].

While the mean BMI was above the 50th percentile in the heart disease cohort, the proportion with obesity was below the national reference. Our data support the findings from Pinto, et al. where the prevalence of obesity was similar for children with and without heart disease [34]. These investigators also found that children who had undergone cardiac surgery had a lower prevalence of obesity compared with children without heart disease, and that this finding was more pronounced in the single ventricle population [34]. While the prevalence of obesity may be lower in children with heart disease, lifestyle counseling should not be ignored since obesity related morbidities may be more deleterious in adult survivors of these conditions [35–38].

Metabolic syndrome was uncommon in this cohort and may be similar to national rates for children. Since there are no well-defined pediatric criteria for the metabolic syndrome, we used cutoff values suggested by the NHLBI and AAP [2, 17]. The National Cholesterol Education Program estimated the prevalence of metabolic syndrome at 4% in the general adult population [17, 39]. The prevalence was similar in this cohort at 5%.

Limitations

Our study represents a single center experience. Lifestyle plays a significant role in the prevalence of CAD risk factors, but specific behaviors that might account for changes within the risk factor profiles were not explored. Additionally, we did not account for ethnic variations within the cohort which could contribute to differences in risk factor profiles [40].

Conclusion

Compared with national reference standards, a higher proportion of subjects with KD, repaired coarctation or severe CHD had hypertension and a low HDL, while a lower proportion had obesity. There was no difference in non-HDL cholesterol. Metabolic syndrome was rare in this cohort. Age was not associated with any CAD risk factor. Based on these results, physicians caring for children with a history of KD, repaired coarctation, or severe heart disease should follow current screening guidelines for dyslipidemia, but should pay particular attention to identifying and treating children with hypertension.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest.

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