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ORIGINAL ARTICLE

Cardiovascular Risk Factors and Carotid Intima-Media Thickness in Asymptomatic Children

Ana Maria Verçoza · Matteo Baldisserotto · Carlos Abaeté de los Santos · Carlos Eduardo Poli-de-Figueiredo · Domingos Otavio d'Avila

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Abstract Atherosclerosis, beginning in childhood, is dependent on several risk factors and may be predictive of coronary artery disease in adulthood. The risk factors for subclinical atherosclerosis are similar to those for clinical disease. Carotid intima-media thickness is a measure of subclinical atherosclerosis and a predictor of subsequent vascular events. This study aimed to examine the relationships of carotid intima-media thickness with known risk factors in asymptomatic children. Family history of cardiovascular disease was collected, together with anthropometric, demographic, and clinical data. Body mass index *z*-scores were calculated. Serum glucose, lipid fractions, fibrinogen, and C-reactive protein were determined. High-resolution ultrasonography was used to assess intima-media thickness. Associations and relationships of risk factors with composite intima-media thickness were explored. The study enrolled 93 children (44 girls) ranging in age from 49 to 169 months. The boys had a thicker intima-media (0.46 ± 0.06 mm) than the girls (0.43 ± 0.06 mm; $p = 0.028$). The unadjusted triglyceride levels were significantly higher in the overweight and obese children ($p = 0.010$). Body mass index and overweight/obesity were positively related to intima-media thickness ($r = 0.259$; $p = 0.012$ and $r_s = 0.230$; $p = 0.027$, respectively), whereas family history of cardiovascular disease was unrelated. Only gender and overweight/obesity were related to intima-media thickness in a multiple linear regression model ($R^2 = 0.125$; $p = 0.002$). Male gender and overweight/obesity were associated with increased intima-media thickness, whereas family history of cardiovascular disease was unrelated.

Keywords Cardiovascular disease · Children · Intima-media thickness · Obesity · Overweight · Risk factor

A. M. Verçoza · C. A. de los Santos · C. E. Poli-de-Figueiredo · D. O. d'Avila (✉)
Programa de Pós-Graduação em Medicina e Ciências da Saúde (Nefrologia), Faculdade de Medicina/IPB/HSL, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Av. Ipiranga, 6690, Porto Alegre, RS 90016-000, Brazil
e-mail: dominavila@pucrs.br

M. Baldisserotto
Programa de Pós-Graduação em Pediatria e Saúde da Criança, Faculdade de Medicina, PUCRS, Serviço de Radiologia, Hospital São Lucas da PUCRS, Porto Alegre, Brazil

Although complications of cardiovascular disease appear late in life, there is evidence that atherosclerosis may start at an early age [21]. Pathologic studies of children and young adults suggest that the process depends on both the number and extent of risk factors identified in childhood that are predictive of adulthood risk for coronary artery disease [2, 3, 14, 20]. Genetic and environmental factors have been associated with atherosclerotic vascular disease [8, 17]. Among such risk factors, family history of cardiovascular disease (CVD) and childhood obesity have been particularly linked to CVD in adulthood [10, 18].

Findings have shown that the risk factors for subclinical atherosclerosis are similar to the risk factors for clinical CVD [8]. Increased carotid intima-media thickness (cIMT) has been taken as evidence of subclinical atherosclerosis and as a strong predictor of subsequent arteriographically documented vascular lesions, myocardial infarction, and stroke [15, 16, 19]. Age, family history of CVD, and obesity have been associated with increased cIMT in children [6, 11, 13, 15]. However, the longitudinal impact of these associations is not fully understood [10, 12].

The current study aimed to examine the relationships linking family history of CVD, overweight/obesity, and other cardiovascular risk factors to cIMT in asymptomatic Brazilian children.

Methods

This cross-sectional study enrolled 93 asymptomatic children undergoing regular health supervision visits at the pediatric clinic of Hospital São Lucas, a university hospital in southern Brazil. The study protocol was approved by the University Research Ethics Committee, and a written consent was obtained from each subject's parents or guardian before enrollment.

To ascertain whether the subjects had a family history of CVD, a standardized questionnaire was presented to parents or guardians with regard to known hypertension or recorded vascular events, as well as unexplained sudden death of a first- or second-degree relative before the age of 55 years among males and 65 years among females [7]. Demographic and anthropometric data were obtained, and body mass index (BMI) was computed. The World Health Organization (WHO) standard definitions for overweight and obesity were followed for classification of the research subjects [25].

Data from a nationally representative cross-sectional Brazilian growth study—part of a large international survey—were used in computing and for age and sex correction of individual BMI *z*-scores, which were used in statistical analyses [4, 5]. Blood pressure determinations followed the established criteria for children [23].

A 2-ml venous blood sample was collected from each subject for biochemical determinations after a 12-h fasting period. Creatinine was measured by an automated Jaffé reaction. Automated enzymatic procedures were used to measure glucose, total cholesterol (T-CHOL), high-density lipoprotein (HDL), and triglycerides (TGL) (Advia 1650; Bayer Health Care, Tarrytown, NY, USA). Low-density lipoprotein (LDL) cholesterol was computed using Friedewald's equation.

Both T-CHOL and HDL were analyzed as quartiles and corrected for age and sex in accordance with National Health and Nutrition Examination Survey (NHANES) III tables [24], whereas LDL and TGL were analyzed as absolute values because percentiles for children younger than 124 months were unavailable. A thrombin-clotting-time-based method was used in fibrinogen determinations (CA-1500, Sysmec, Kobe, Japan), and C-reactive protein (CRP) was measured by immunonephelometry (BN II Analyzer; Dade Behring, Deerfield, IL, USA).

All the ultrasound scans and cIMT measurements were performed by a single investigator (M.B.). The between-visit mean coefficient of variation for the cIMT of all vessels was 6.2%. The internal carotid artery, carotid bulb, and common carotid artery were examined on both sides with a 12–5 MHz linear transducer and ultrasound equipment (HD-11; Philips Medical Systems, Bothell, WA, USA) using different scanning angles to identify the greatest wall thickness. Longitudinal images through the center of each vessel were obtained, and the wall thickness was measured in video-printed images (UP-20; Sony, Tokyo, Japan).

For this study, cIMT was measured as the distance between the interface of the lumen and the intima and as the interface between the media and the adventitia. The maximal cIMT was computed at each scanned vessel segment. A strong correlation between each individual segment and the composite mean cIMT was evidenced. Only the composite cIMT was used in statistical analyses.

Continuous variables are presented as means ± standard deviations or as medians and interquartile ranges. Categorical variables are presented as frequency, percentage, or ratio. Continuous variables with a normal distribution were compared by the Student's *t* test and those with an asymmetric distribution by the Mann–Whitney *U* test. The chi-square (χ^2) test or Fisher's exact test was used to compare categorical variables. The Kruskal–Wallis test was used to evaluate possible differences in the distribution of overweight/obesity and cIMT by four different age strata. Pearson's and Spearman's correlation coefficients were used to evaluate associations between two variables. A multiple linear regression analysis (forward) model was used to evaluate possible risk factors associated with cIMT. Differences were considered significant at a p value of 0.05 or less.

Statistical Package for Social Sciences software (SPSS, version 11.5 for Windows, SPSS Inc, Chicago, IL, USA) was used for all the statistical analyses.

Results

The age of the enrolled subjects ranged from 49 to 169 months. No significant differences in cIMT or in anthropometric, demographic, clinical, or laboratory data were apparent between subjects with or without a family history of CVD. In terms of weight, 41 of the participants were overweight (19%) or obese (25%). No differences in the distribution of overweight/obesity or cIMT by stratified age were observed. The girls presented with significantly lower glucose levels (4.51 ± 0.38 vs 4.73 ± 0.41 mmol/l; $p = 0.027$), whereas the boys had a greater cIMT (0.46 ± 0.06 vs 0.43 ± 0.06 mm; $p = 0.028$).

The age of the subjects had no apparent effect on cIMT, neither in correlation nor in evaluation differences at four different age strata. The systolic or diastolic blood

pressures of 15 subjects (7 with normal BMI and 8 overweight or obese) were above the 95th percentile, with no significant difference between groups. Levels of T-CHOL and HDL at the 95th percentile or above occurred for seven and four subjects, respectively, with no significant differences between the children at normal weight and those overweight or obese. Levels of TGL, unadjusted for age or sex, were significantly higher in overweight or obese children, whereas CRP levels above 3 mg/l were more prevalent among children with a positive family history for CVD (16/55 vs. 4/38; $p = 0.003$). Overweight and obese children had thicker intima-media layers. The characteristics of the study population are depicted in Table 1.

The BMI z-score correlated positively with fibrinogen ($r = 0.254$; $p = 0.014$), systolic blood pressure ($r = 0.296$; $p = 0.004$), diastolic blood pressure ($r = 0.301$; $p = 0.003$), and cIMT ($r = 0.2959$; $p = 0.012$). Systolic blood pressure correlated with cIMT ($r = 0.256$; $p = 0.012$). Overweight/obesity correlated positively with quartiles of TGL ($r_s = 0.297$; $p = 0.004$) and cIMT ($r_s = 0.230$; $p = 0.027$), and negatively with quartiles of HDL ($r_s = -0.249$; $p = 0.017$). Quartiles of T-CHOL correlated with quartiles of HDL ($r_s = 0.251$; $p = 0.018$) and TGL ($r_s = 0.468$; $p < 0.001$). Quartiles of HDL correlated negatively with overweight/obesity ($r_s = -0.249$; $p = 0.017$). Tables 2 and 3 depict Pearson's and Spearman's correlation coefficients, respectively.

Only gender and overweight/obesity related to cIMT in a multiple linear (forward) regression model that included the variables of age, gender, family history of CVD, triglycerides, BMI z-score, and overweight/obesity ($R^2 = 0.125$; $F = 6.416$; residual standard deviation = 0.00007;

Table 1 Anthropometric, clinical, and laboratory characteristics

Variable	Total ($n = 93$)	Normal weight ($n = 52$)	Overweight/obese ($n = 41$)
Mean age (months)	106 ± 29	104 ± 28	109 ± 30
Caucasian: *n* (%)	78 (84)	43 (83)	35 (85)
Male: *n* (%)	49 (53)	27 (52)	22 (54)
Mean BMI (kg/m^2)	18.9 ± 5.1	15.6 ± 1.7*	22.7 ± 5.1*
Family history of CVD: *n* (%)	55 (60)	29 (56)	26 (63)
Mean DBP (mmHg)	68 ± 10	66 ± 10	70 ± 10
Mean SBP (mmHg)	109 ± 14	107 ± 15	109 ± 12
Mean composite cIMT (mm)	0.44 ± 0.07	0.43 ± 0.06**	0.46 ± 0.08**
Mean fibrinogen (μmol/l)	8.40 ± 2.06	7.97 ± 2.03	8.76 ± 2.03
Mean glucose (mmol/l)	4.61 ± 0.40	4.60 ± 0.37	4.62 ± 0.45
Mean HDL (mmol/l)	1.37 ± 0.40	1.42 ± 0.34	1.29 ± 0.26
Mean LDL (mmol/l)	2.32 ± 0.74	2.28 ± 0.83	2.56 ± 0.67
Mean T-CHOL (mmol/l)	4.11 ± 1.16	4.09 ± 1.14	4.22 ± 0.78
Median triglycerides: mmol/l (IQR)	0.76 (0.55–1.03)	0.67 (0.47–0.87)#	0.89 (0.80–1.02)#

BMI body mass index; *CVD* cardiovascular disease; *DBP* diastolic blood pressure; *SBP* systolic blood pressure; *cIMT* carotid intima-media thickness; *HDL* high-density lipoprotein cholesterol; *LDL* low-density lipoprotein cholesterol; *T-CHOL* total cholesterol; *IQR* interquartile range

* $p < 0.001$, Student's t-test

** $p = 0.023$, Student's t-test

$p = 0.010$, Mann–Whitney test

Table 2 Pearson's correlation coefficients (p value)

	Age	Glucose	Fibrinogen	DBP	SBP	BMI z-score	Composite cIMT
Age	1.0	0.200 (0.054)	−0.102 (0.331)	−0.020 (0.850)	−0.014 (0.895)	0.001 (0.995)	0.132 (0.206)
Glucose	0.200 (0.054)	1.0	0.051 (0.150)	0.001 (0.999)	0.126 (0.227)	0.151 (0.150)	0.113 (0.279)
Fibrinogen	−0.102 (0.331)	0.051 (0.150)	1.0	0.008 (0.938)	0.092 (0.383)	0.254 (0.014)	0.082 (0.433)
DBP	−0.020 (0.850)	0.001 (0.999)	0.008 (0.938)	1.0	0.772 (<0.001)	0.301 (0.003)	0.107 (0.307)
SBP	−0.014 (0.895)	0.126 (0.227)	0.092 (0.383)	0.772 (<0.001)	1.0	0.296 (0.004)	0.256 (0.013)
BMI z-score	0.001 (0.995)	0.151 (0.150)	0.254 (0.014)	0.301 (0.003)	0.296 (0.004)	1.0	0.259 (0.012)
Composite cIMT	0.132 (0.206)	0.113 (0.279)	0.082 (0.433	0.107 (0.307	0.256 (0.013)	0.259 (0.012)	1.0

DBP diastolic blood pressure; *SBP* systolic blood pressure; *BMI* body mass index; *cIMT* carotid intima-media thickness

Table 3 Spearman's correlation coefficients (*p* value)

	Gender	CVD	CRP	T-CHOL	HDL	TGL	Overweight/obesity	Composite cIMT
Gender	1.0	0.045 (0.670)	−0.062 (0.554)	−0.129 (0.226)	−0.129 (0.219)	−0.059 (0.572)	0.047 (0.655)	0.193 (0.063)
CVD	0.045 (0.670)	1.0	0.231 (0.026)	−0.135 (0.206)	−0.068 (0.521)	−0.141 (0.178)	0.082 (0.435)	−0.043 (0.681)
CRP	−0.062 (0.554)	0.231 (0.023)	1.0	0.098 (0.360)	−0.094 (0.371)	−0.068 (0.519)	0.027 (0.800)	0.113 (0.280)
T-CHOL*	−0.129 (0.226)	−0.135 (0.206))	0.098 (0.360)	1.0	0.251 (0.018)	0.468 (<0.001)	0.087 (0.414)	0.060 (0.573)
HDL*	−0.129 (0.219)	−0.068 (0.521))	−0.094 (0.371)	0.251 (0.018)	1.0	−0.010 (0.927)	−0.249 (0.017)	−0.029 (0.784)
TGL	−0.059 (0.572)	−0.141 (0.178)	−0.068 (0.519)	0.468 (<0.001)	−0.010 (0.927)	1.0	0.297 (0.004)	0.043 (0.682)
Overweight/obesity	0.047 (0.655)	0.082 (0.435))	0.027 (0.800)	0.087 (0.414)	−0.249 (0.017)	0.297 (0.004)	1.0	0.230 (0.027)
Composite cIMT	0.193 (0.063)	−0.043 (0.681))	0.113 (0.280)	0.060 (0.573)	−0.029 (0.784)	0.043 (0.682)	0.230 (0.027)	1.0

CVD cardiovascular disease; *CRP* C-reactive protein; *T-CHOL* total cholesterol; *HDL* high-density lipoprotein cholesterol; *TGL* triglycerides; *cIMT* carotid intima-media thickness

$p = 0.002$; cIMT = 0.414 + 0.022 * overweight/obesity + 0.028 * gender).

Discussion

The boys in this study had thicker arterial walls than the girls. The TGL levels and cIMT were significantly higher in overweight and obese children. No association between family history of CVD and other cardiovascular risk factors (except for increased CRP levels) or cIMT were found. Overweight/obesity was prevalent and related to cIMT.

Although a previous study showed an age-related increase in cIMT among healthy children, such a trend was not evident in the current study [11]. Independently of age or overweight/obesity, the boys had thicker carotid arteries than the girls. Gender was an independent predictor of cIMT. Such findings had not been previously disclosed for prepuberal children, yet the intima-media seemed to be thicker in adolescent, young, and older adult males than in females [1, 22, 24].

In a previous study, children with a positive parental history of premature myocardial infarction had a greater cIMT than children with a corresponding negative family history [6]. In a randomly selected cohort, young adults with a positive family history of CVD had increased cIMT. Components of the metabolic syndrome also were more prevalent [6, 13].

Contrary to these findings, no significant differences or associations between children with or without family history of CVD were demonstrated in the current study. However, study populations diverge significantly. The current study population was younger, with family histories of early vascular events encompassing episodes other than parental myocardial infarction, which possibly explains the differences [6]. Furthermore, ethnic characteristics may set Finnish and Brazilian study populations apart. Finally, it is not inconceivable that the addition of other risk factors may be necessary for the appearance of vascular changes dependent on genetic factors.

The association of BMI *z*-scores and overweight/obesity with increased cIMT is in agreement with recent observations [1, 26]. Interestingly, overweight/obese children also had significantly higher TGL levels, suggesting raised insulin levels. However, the mean LDL level, apparently an early predictor of adult atherosclerosis, was not significantly higher [13, 24]. Although increased cIMT in children and adolescents has been taken as a biomarker of augmented risk for cardiovascular events later in life, that course may not necessarily be a mandatory outcome [1, 15]. Longitudinal cohort studies suggest a significant tracking of body mass from youth to adulthood, thus

significantly reducing the impact of childhood overweight or obesity on adult cIMT and cardiovascular risk [10, 13].

Furthermore, cIMT was not increased in nonobese adults that had been obese children nor in obese adults that had been slender children, again suggesting the need for a cumulative effect of obesity [9]. Possibly, other risk factors such as high LDL level, smoking, and hypertension must add to obesity over time to promote endothelial activation and atherosclerosis in adult life [15].

The finding that the BMI *z*-score correlated positively with cIMT and was a predictor of cIMT in a linear multivariate regression model is in accordance with several previous studies, suggesting that obesity may be the single most important factor associated with increased cIMT in childhood [1, 15, 22]. However, the relationship of this finding with adulthood atherosclerotic disease remains uncertain [13].

This was an observational study of possible risk factors associated with cIMT among children living in an urban community of southern Brazil. A representative sample of the population in this area—mostly Caucasian subjects, with a significant proportion of German and Italian descendants—comprised the study population. Different from surveys that have evaluated only the offspring of individuals with premature myocardial infarction, the current study took into account cardiovascular events occurring in families of the enrolled children up to second-degree relatives. Despite an increased number of cardiovascular events, the power to find associations with a family history of CVD may have been lessened. Additionally, family history of CVD was assessed by questionnaire.

In summary, the boys in a selected study population of prepuberal Brazilian children had increased carotid artery wall thickness. Gender, overweight/obesity, and BMI were related to cIMT, but not family history of CVD. A study with a larger cohort should be undertaken to evaluate the current findings prospectively.

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