Original Article

Ultrasound Evaluation of Carotid Intima-Media Thickness in Children

Matias Epifanio[1], Matteo Baldisserotto[1], Edgar E. Sarria[1, 2], Arthur Lazaretti[1] and Rita Mattiello[1]

[1]School of Medicine and Post-Graduate Program in Pediatrics/Child Health, Pontifícia Universidade Católica do Rio Grande do Sul, Brazil
[2]School of Medicine, Universidade de Santa Cruz do Sul, Brazil

***Aim*: The purpose of this study was to assess the association with automated US measurements of carotid artery intima-media thickness (cIMT) with anthropometric, laboratory data and ultrasonographic measurements of fat, in order to identify potential markers that could be used to prevent the development and progression of cardiovascular pathology in adolescents.**
***Method*: Forty-five patients aged 10 to 17 years were enrolled in this study. Blood samples and anthropometric measurements were obtained from all subjects. All patients underwent an ultrasonic assessment of subcutaneous tissue, pre-peritoneal fat, and intra-abdominal fat. All patients received an US assessment of the common carotid artery intima-media thickness.**
***Results*: There was a positive association of minimum beds of pre-peritoneal fat, on both sides, with cIMT. Additionally, cIMT on the right side was positively associated with HOMA-IR. In our multivariate analysis, HOMA-IR remained independently associated with cIMT (left) and measurement of the minimum bed of pre-peritoneal fat was associated with right cIMT. There was no association of cIMT with sex, BMI z-score, demographic variables or laboratory findings.**
***Conclusion*: Pre-peritoneal fat and HOMA-IR are associated with automated ultrasound measurements of both carotid intima-media thickness. Carotid intima-media thickness was not associated with any other demographic variables nor with other laboratory findings when assessed with our automated US method.**

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Key words: Carotid Intima-Media Thickness, Atherosclerosis, Skinfold Thickness

Introduction

Atherosclerotic disease is a major cause of morbidity and mortality worldwide and can develop silently for decades before the occurrence of clinical events[1)]. From its earliest phases, atherosclerosis is related to the presence and intensity of known cardiovascular risk factors[2, 3)]. Recent attention has been focused on applying preventive measures for atherosclerosis beginning in childhood to reduce the risk of heart disease, stroke, and peripheral vascular disease later in life[4)].

New imaging technologies have enabled us to monitor progression of arterial wall disease more accurately and efficiently[5)]. Measurement of carotid artery intima-media thickness (cIMT) by ultrasonography is a feasible approach that is direct, noninvasive, and has good correlation with histology in the assessment and detection of preclinical lesions of the arterial wall[2, 6)]. Thickening of the intima and media layers of the carotid artery provides predictive information in addition to traditional cardiovascular risk factor assessment. As a clinical and research instrument, cIMT measurement can be used to evaluate cardiovascular risk and to access the intervention effects on the subclinical atherosclerosis grade[7)].

Address for correspondence: Matias Epifanio, School of Medicine and Post-Graduate Program in Pediatrics/Child Health, Pontifícia Universidade Católica do Rio Grande do Sul, Brazil
Primeiro de Janeiro n 150 Ap 1804.CEP 90470320. Porto Alegre Brazil
E-mail: mepifanio@hotmail.com
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Atherogenesis can be attributed to a generalized disturbance of endothelial function, and cIMT provides an index of coronary disease[8]. Although studies have shown significantly increased cIMT in children with type 1 diabetes, hypertension, and/or familial hypercholesterolemia, cIMT data in obese children are less clear[6]. The American Heart Association recommends cIMT measurement for evaluating the risk for developing cardiovascular disease in intermediate-risk adult patients (according to Framingham risk score) and in high-risk pediatric patients as well[8].

Obesity in childhood has reached epidemic proportions; it is associated with hypertension, glucose intolerance, and inflammation markers in chronic adults and children[6, 9]. Furthermore, these clinical findings appear to be causally related to the initiation and progression of proatherogenic vascular changes, even in juveniles. Morphological and functional changes of the vascular wall are accepted universally as early and essential steps in the development of atherosclerosis, and the detection of increased cIMT may reflect such structural changes[6, 10]. Whether the thickness of the arterial wall increases with body mass index (BMI) remains a matter of debate[11, 12].

In practice, cIMT is most commonly measured manually in an ultrasound (US) examination. However, this method is time consuming and the results may be affected by the operator's experience or subjective judgment. Relative to manual measurement, automated measurement is faster and associated with less variability for all carotid segments, although both methods are reliable for the measurement of carotid thickness[4, 5, 13] Few studies have evaluated how well automated US measurements of cIMT associate with anthropomorphic measurements and laboratory data in juveniles.

Visceral fat thickness, as measured by US examination, has been consistently correlated with total visceral fat and cardiovascular risk factors. In multiple regression models, the addition of US measurements improved estimates of visceral and subcutaneous fat compared with the contribution of standard anthropometric variables. Furthermore, US measurements may associate better with cardiovascular risk factors than do values derived from anthropometric measurements[14, 15].

In this study, we examined how closely automated US measurements of cIMT associated with anthropometric, laboratory data, and visceral fat thickness measurements in a group of adolescents. Our aim was to identify potential markers of automated US evaluation of cIMT that could be used to indicate intervention to prevent the development and progression of cardiovascular pathology in pediatric patients.

Materials and Methods

Subjects

Two groups of healthy volunteer subjects, 6–17 years of age, were enrolled in this study. The subjects were divided into two groups: (1) an obese group meeting the criterion for obesity according the BMI z-score for Brazilian children and adolescents and (2) a eutrophic group consisting of subjects with BMIs not meeting the criterion for obesity[16]. The exclusion criteria were hepatorenal disease, use of potentially hepatotoxic or nephrotoxic drugs, and chronic disease such as hypertension or diabetes mellitus. Subjects were evaluated in a pediatric outpatient clinic at either the Instituto da Criança da Universidade de São Paulo in São Paulo or the Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul in Porto Alegre. This research project was approved by the Research Ethics Committees of both institutions, and parents or legal guardians provided informed consent.

Measurements

The individuals were weighed and measured according to standardized procedures while barefoot and wearing only light clothing. For body weight determination, we used a mechanical Filizola® brand scale with a coupled stadiometer previously calibrated; BMI was conventionally calculated [body weight (kg)/height (meters)^2]. Each subject's waist circumference (WC) was the average of two measurements using an anthropometric fiberglass tape at the midpoint between the last rib and the iliac crest.

We obtained blood samples from all subjects after 12 h of fasting to measure glycemia, triglyceride (TG), total cholesterol (TC), HDL-cholesterol (HDL), LDL-cholesterol (LDL), insulin, and apolipoprotein B (apoB) levels; TC, HDL, and TG levels were measured enzymatically, and LDL levels were calculated using the Friedewald formula. TC, LDL, HDL, and TG values were stratified by percentile according to age and sex. Insulin and apoB levels were determined by chemiluminescence and automated immunonephelometry, respectively.

We calculated the patients' HOMA-IR index, a mathematical model that quantifies insulin resistance based on the formula: HOMA-IR = fasting insulin (μUI/mL) × fasting glucose (mmol/L)/22.5. All patients had their common cIMT measured by US[17].

Ultrasonographic Measurement

Ultrasonographic measurement of cIMT was

performed digitally over a 1-cm segment of the artery located below the carotid artery bulb with a specially designed computer program (Philips Qlab 6.0). The automated tool measured multiple cIMT data points within several seconds, and yielded the following results for each measurement: mean, maximum, minimum, standard deviation (SD), number of acquired data points, and distance. All studies were performed according to a standardized scanning protocol for the right and left common carotid arteries. The image was focused on the posterior - the far - wall. Three angles were used at each side for scanning the common cIMT: lateral, anterioroblique, and anterior. All images were obtained by the same single, experienced radiologist blinded to the patients' metabolic state. The commercial software algorithm is based on a comprehensive analysis of the two-dimensional vessel structure represented in an US image, rather than on simple detection of grayscale gradients. This technique detects interfaces accurately with negligible influences by random image irregularities. The operator sets the starting and ending point of the measurement area manually and then the two lines along the boundaries of the cIMT are drawn automatically[18].

We performed US examinations using an HD11 Philips equipment (Philips Medical Systems, Bothell, WA). The transducer was placed on the skin gently to avoid compressing the fat beds. US measurements of the subcutaneous, preperitoneal, and visceral abdominal fat were performed with patients lying in a supine position. A 7.5e10-MHz linear transducer was maintained perpendicular to the skin in the upper middle abdominal region as we performed each exam longitudinally from the xiphoid process to the umbilical region across the length of the linea alba, taking care that the surface of the liver was nearly parallel to the skin.

Maximum subcutaneous fat thickness (Smax) was measured 5 cm from the umbilicus on the umbilical line. Minimum subcutaneous fat thickness (Smin) was measured immediately below the xiphoid process. We performed measurements directly from the screen using an electronic caliper on the skin−fat interface (excluding the skin) and on the muscle−fat interface and then measured the average thickness. Measurements of the maximum and minimum beds of preperitoneal fat (Pmax and Pmin, respectively) were performed in the region where the fat was most easily visualized, i.e., immediately below the xiphoid process between the internal side of the linea alba and the surface of the liver. Finally, we used a 3.5e5.0-MHz curvilinear transducer to measure the thickness of the visceral fat bed, commonly referred to as IAF, between the internal side of the abdominal muscle and the anterior wall of the aorta.

To assess intraobserver agreement, one experienced radiologist (MB) performed two measurements, separated by an interval of 1 week, in a group of patients. When performing the second measurement, the observer was blinded to the results of the first measurement.

Statistical Analysis

Demographic data are reported as means ± SDs for parametric variables or as medians with interquartile ranges for non-normally distributed variables. Generalized linear models were used to analyze the relationship between the main outcome (cIMT) and the predictor variables (sex, age, height, weight, BMI z-score, WC, and HOMA-IR index). The Wald's test was used to assess statistical significance. Initially, all covariates that presented $p < 0.15$ in the univariate model were included in the multivariate model. The next step was the individual exclusion of the covariates that presented critical p values (values that were not significant). This step was repeated until all variables remaining in the model presented $p < 0.05$. All analyses were performed using SPSS v.18 software (SPSS Inc., Chicago, IL).

Results

The demographic, clinical characteristics, and US measurements of abdominal fat of the enrolled subjects are summarized in **Table 1**. The majority was female, mean BMI was 27.23 ± 8.46 kg/m^2, and mean age was 13.06 ± 2.34 years. About two-thirds of the subjects in the study had TC and LDL levels below the 75th percentile (considered acceptable for their age). However, nearly half of the subjects had HDL levels above the 50th percentile for their sex and age, and nearly a third had TG levels above the 75th percentile. Mean right and left cIMT was 0.457 and 0.445, respectively.

The intraclass correlation coefficient (ICC) for total fat was 0.961, with a 95% confidence interval (CI) of 0.851 e 0.990.

According to the univariate analysis, cIMT on both the right and the left sides was found to positively associate with Pmin. In the multivariate analysis, none of the other demographic variables, laboratory findings, or US measurements were significantly associated with cIMT. Additionally, cIMT on the right side was found to positively associate with HOMA-IR (**Table 2**). In the multivariate analysis, HOMA-IR remained independently associated with cIMT (right

Table 1. Patient characteristics ($n = 45$)

Characteristic	Value
Sex (females), n (%)	24 (53.3)
Nutritional status (Obese), n (%)	25 (55.5)
Height (m), mean ± SD	1.61 (0.09)
Age (years), mean ± SD	13.06 ± 2.34
BMI (kg/m^2), mean ± SD	27.23 ± 8.46
BMI (z-score), median (interquartile range)	2.69 (−0.15 to 3.26)
WC (cm), mean ± SD	90 ± 20
ApoB (g/L), mean ± SD	0.63 ± 0.15
TC (patients below 75th percentile[a]), n (%)	29 (64.4%)
HDL (patients above 50th percentile), n (%)	20 (46.5%)
LDL (patients below 75th percentile[a]), n (%)	31 (68.8%)
TG (patients above 75th percentile), n (%)	14 (32.5%)
Insulin (pmol/L), mean ± SD	13.3 ± 9.98
Glucose (mmol/L), mean ± SD	4.73 ± 0.40
HOMA-IR, mean ± SD	2.96 ± 2.57
Right cIMT (mm), mean ± SD	0.457 ± 0.04
Left cIMT (mm), mean ± SD	0.445 ± 0.04

[a]considered acceptable for age.
Abbreviations: SD, standard deviation; BMI, body mass index; WC, waist circumference; ApoB: apolipoprotein B; TC: total cholesterol; HDL, HDL-cholesterol; LDL, LDL-cholesterol; TG, triglycerides; HOMA-IR, homeostasis model assessment of insulin resistance; cIMT, carotid intima-media thickness.

and left), and Pmin was associated with left cIMT (**Table 3**).

Discussion

In this study, we found that HOMA-IR and Pmin were positively associated with cIMT; in the multivariate analysis, none of the other demographic variables or laboratory findings significantly associated with cIMT.

The lack of association between BMI and cIMT is consistent with several studies. Tounian *et al.* did not find a significant difference in cIMT size between 48 severely obese French children and 27 healthy controls[19]. In a cross-sectional study of 5−16-year-old Canadian children, no measure of adiposity was found to be predictive of cIMT[20]. Similar findings have been reported by other researchers, including Aggoun *et al.*[21]. Nevertheless, in a systematic review of 26 observational studies, 22 of the reviewed studies reported a significantly increased cIMT in obese children and adolescents compared with the control group[2]. In some of these studies, a strong association between cIMT and blood pressure was reported, but some of the studies included obese children with hypertension or with blood pressure values significantly higher than their referents[11].

Previous studies have demonstrated cIMT in adults to be highly dependent on age and sex[22, 23]. However, we did not find an association of cIMT with sex or age in our juvenile subjects. Our negative findings in this regard are consistent with a prior study examining a large cohort of normal children and young adults in which cIMT was found not to be affected by age or sex until 18 years of age[24]. McCarthy and Ashwell found WC to be a highly sensitive and specific marker of upper body fat accumulation in children[25], and several other studies have shown WC to be associated with carotid artery dimensions[9, 12, 26, 27]. In a study of Turkish children employing linear logistic regression, Hacihamdioğlu *et al.* found that WC was the only parameter associated with increased cIMT[28]. They concluded that children with abdominal obesity are at increased risk for atherosclerosis and that WC can be used to screen for atherosclerosis risk in obese children[28]. In our study, WC was associated with cIMT on the right side in the univariate analyses, but it did not remain significant after adjusting for other variables. Our univariate analysis revealed that HOMA-IR on the right side and Pmin in both sides were positively associated with cIMT, associations and variables that persisted in our multivariate analysis.

Table 2. Univariate analysis results for association of right and left cIMT measured by US with anthropometric and clinical findings

Variable	*cIMT (R)*	*p*	*cIMT (L)*	*p*
BMI z-score	0.003 (−0.003 to 0.009)	0.290	0.000 (−0.006 to 0.005)	0.831
WC:H	0.055 (−0.032 to 0.142)	0.219	−0.009 (−0.100 to 0.081)	0.838
CIx	0.40 (−0.058 to 0.002)	0.423	−0.012 (−0.112 to 0.089)	0.822
HOMA-IR	0.007 (0.002 to 0.012)	0.004*	0.003 (−0.003 to 0.008)	0.314
Pmax	0.002 (0.001 to 0.002)	0.419	0.002 (0.001 to 0.002)	0.976
Smin	0.002 (0.001 to 0.002)	0.078	0.002 (0.001 to 0.002)	0.943
Pmin	0.002 (0.001 to 0.002)	0.006*	0.056 (0.016 to 0.096)	0.006*
Smax	0.002 (0.001 to 0.002)	0.197	0.002 (0.001 to 0.002)	0.837
IAF	0.002 (0.001 to 0.002)	0.151	0.002 (0.001 to 0.002)	0.913
Total Fat	0.003 (−0.001 to 0.006)	0.101	0.000 (−0.003 to 0.0004)	0.908

Abbreviations: US, ultrasonography; BMI, Body Mass Index; WC:H, the ratio between WC and height; CIx, conicity index; HOMA-IR, homeostasis model assessment of insulin resistance; Pmax, maximum preperitoneal fat; Smax, maximum subcutaneous fat thickness; Pmin, minimum preperitoneal fat; Smin, minimum subcutaneous fat thickness; IAF, intra-abdominal fat.

Suzuki *et al*. found that insulin resistance was the most significant risk factor for cIMT in a study of 72 adult patients[29]. Additionally, in a study examining overweight Turkish children, Yilmazer *et al*. found that hyperinsulinemia correlated with increased cIMT[27]. Similar findings have been obtained in other studies[6, 9, 13, 26, 28], although some studies found no association between cIMT and HOMA-IR[30, 31].

Various studies have demonstrated discrepancies between the intima-media thicknesses measured on the left and right common carotid arteries[32] and emphasized the importance of measuring and reporting values from both sides when conducting cIMT studies[33-35]. Atherosclerotic lesions may develop earlier on the left side than the right side because of the anatomical configuration of the left carotid artery, which originates directly from the aortic arch and, therefore, may be exposed to greater shear stress than the right carotid artery. Indeed, shear stress has been shown to influence the location and rate of development of atherosclerotic lesions[33]. Interestingly, Luo and colleagues demonstrated that right cIMT correlates primarily with hemodynamic parameters, whereas left cIMT correlates better with biochemical indices (such as TC, LDL-C, and the blood glucose level)[34]. However, in our univariate analysis, the HOMA-IR index (which is calculated from serum glucose and insulin values) was associated with cIMT on the right side only, indicating a relationship between right cIMT and biochemical parameters.

The present study is different from most prior work in that we measured cIMT using an automated US tool; most prior studies of cIMT in obese subjects were conducted by a manual measurement method. Manual cIMT measurement (point-to-point measurement of B-mode images) is also the most common technique used in clinical practice, although it is time consuming and the results may be compromised by lack of expertise or the subjective judgment of the observer[5], resulting in clinically important inter- and intraobserver variability[18]. The development of automated methods for measuring cIMT in a standard US equipment can reduce the duration of the US examination and lead to better reproducibility of results across observers. The automated method also enables new data to be compared to previously published data for different populations according to percentiles[5]. Furthermore, the new system should prevent the problem of measurement drift over time[36]. The differences between our findings and prior findings may be due, at least in part, to the use of automated versus manual measurement techniques.

Our study has some limitations. First, our sample size limits the power of some of the analyses. Second, no functional measure of insulin resistance was available in our study. Functional methods provide precise quantitative measures of insulin resistance, but they are costly, challenging to perform, moderately invasive, and are best suited for studies involving tens to hundreds of individuals; thus, they are still impractical for routine clinical use[37]. Conversely, the main limitation of prior studies on cIMT in juveniles has been the heterogeneity of the US measurement protocols; indeed this heterogeneity may explain the wide ranges of cIMT values observed[38]. We used an automated protocol for measuring cIMT with the intention of contributing to future homogenization of these data.

On the basis of the present findings, we can conclude that HOMA-IR and Pmin are associated with automated US measurements of both cIMT. cIMT

Table 3. Multivariate analysis between the HOMA-IR index, minimum preperitoneal fat, and carotid intima-media thickness

Variable	*cIMT (R)*	*p*	*cIMT (L)*	*p*
HOMA-IR	0.007 (0.002 to 0.012)	0.004	0.007 (0.001 to 0.012)	0.016
Pmin			0.011 (0.000 to 0.022)	0.049

Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; Pmin: minimum preperitoneal fat; cIMT: carotid intima-media thickness; R: right; L: left.

was not associated with any other demographic variables or with other laboratory findings when assessed by our automated US method. Nevertheless, this method may be useful to evaluate the inflammatory process in association with childhood obesity. Further studies are warranted on a prospective basis to evaluate the potential clinical value of this measure.

Conflicts of Interest

The authors have no commercial associations or sources of support that might pose a conflict of interest.

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