a r t i c l e

Endothelial wall thickness, cardiorespiratory fitness and inflammatory markers in obese and non-obese adolescents

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ABSTRACT | Background: Increased carotid intima-media thickness (c-IMT) is considered a marker of early-onset atherosclerosis and it has been found in obese children and adolescents, but the risk factors associated with this population remain to be elucidated. **Objective**: To compare and verify the relationship between c-IMT, metabolic profile, inflammatory markers, and cardiorespiratory fitness in obese and non-obese children and adolescents. **Method**: Thirty-five obese subjects (19 boys) and 18 non-obese subjects (9 boys), aged 10-16 years, were included. Anthropometry, body composition, blood pressure, maximal oxygen consumption (VO_2max), and basal metabolic rate were evaluated. Serum glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), blood lipids, C-reactive protein (CRP), and adiponectin were assessed. c-IMT was measured by ultrasound. **Results:** The results showed that c-IMT, triglycerides, insulin, HOMA-IR, and CRP values were significantly higher in the obese group than in the non-obese group, and high-density lipoprotein cholesterol (HDL-c), adiponectin, and VO_2max values were significantly lower in the obese group than in the non-obese group. The c-IMT was directly correlated with body weight, waist circumference, % body fat, and HOMA-IR and inversely correlated with % free fat mass, HDL-c, and VO_2max. **Conclusions**: Our findings show that c-IMT correlates not only with body composition, lipids, insulin resistance, and inflammation but also with low VO_2max values in children and adolescents.

Keywords: obesity; inflammation; atherosclerosis; adolescents; fitness; physical therapy.

HOW TO CITE THIS ARTICLE

Introduction

Obesity is independently associated with coronary atherosclerosis in young adults[1]. Inflammation, obesity, and insulin resistance usually occur together, as they are part of the atherosclerotic process and contribute to the development of cardiovascular diseases[2]. Research in the juvenile population shows a relationship between inflammatory markers and endothelial dysfunction[3,4]. The elevation of C-reactive protein (CRP) is considered an indicator of inflammation and a predictor of cardiovascular diseases and diabetes[5]. Low concentrations of adiponectin are associated with obesity[6,7], vasculopathy, and diabetes[8].

Recently, non-invasive techniques have been used in order to evaluate early markers of atherogenesis, including ultrasound assessment of the wall thickness of the endothelium[9,10]. This evaluation consists in measuring, by means of ultrasound imaging, the thickness of the tunica intima and tunica media of the artery[9], known as intima-media thickness (IMT). The increase in this value is considered a risk factor for coronary artery disease[10] and current data shows that obese children have greater carotid intima-media thickness (c-IMT) than healthy children, thus suggesting that they are more susceptible to cardiovascular events in adulthood[2,3,9].

Some studies have examined the c-IMT in children and adolescents[2,3], but few studies also verified cardiorespiratory fitness[11]. The diagnosis and prevention of these risk factors in childhood are important public health issues, as they allow early intervention in individuals at a higher risk of developing cardiovascular diseases during the juvenile or adult phase. Therefore, the objective of this paper was to investigate the relationships among endothelial

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dysfunction, dyslipidemia, level of cardiorespiratory fitness, and inflammatory markers in obese and non-obese subjects.

Method

Participants

The sample included 53 subjects, aged 10-16 years of age, from the city of Curitiba, PR, Brazil. Participants were divided into two groups, the obese group (n=35) and the non-obese group (n=18). Inclusion criteria were: a) informed consent signed by parents or guardians, b) meeting the criteria for obesity and non-obesity described below, and c) no history of regular physical activity outside of physical education classes at school. Based on body mass index (BMI) and U.S. growth charts[12], participants were classified as obese (n=35, BMI>P95%) and non-obese (n=18, BMI<85%). The obese group was selected among participants from an intervention project conducted at Universidade Federal do Paraná (UFPR), Curitiba, PR, Brazil. The non-obese group consisted of volunteers from public schools matched by sex and age. Exclusion criteria consisted of: a) musculoskeletal problems or physical disability, b) subjects who did not undergo all assessments, c) subjects with abnormal thyroid-stimulating hormone (TSH) function. All of the adolescents and their legal guardians gave written informed consent. The study complied with Resolution 196/96 of the National Health Council and was previously approved by the Human Research Ethics Committee of the UFPR Health Sciences Faculty (CEP/SD: 945.070.10.06).

Variables

Clinical evaluation

Chronological age (CA) was recorded to the nearest 0.1 year by subtracting the birth date from the date of the mid-testing period. Sexual maturation was given by stages of pubic hair (PH) and was individually assessed following the criteria described by Tanner[13]. Resting heart rate (HRres) and systolic (SBP) and diastolic blood pressure (DBP) were measured with the subjects in the sitting position after 10 minutes of rest. HRres was obtained using a heart rate monitor (Polar A2) followed by blood pressure (BP), which was always measured by a single clinician in the right arm supported at heart level, using a mercury sphygmomanometer (Wan Med®, São Paulo, SP, Brazil). Two measurements were

taken, with an interval of 2 minutes between them. The lowest value was considered for the analysis. BP measurements were considered as borderline or increased if the values were equal to or above the 90th percentile for age and sex[14].

Anthropometry

Height was measured with a portable stadiometer (Harpenden, Holtain Ltd, Crosswell, Crymych, Pembs., UK) to the nearest 0.1 cm. Body mass was measured with a portable scale (Seca 770, Hanover, MD, USA) to the nearest 0.1 kg. Anthropometry was performed by a single individual following standardized procedures[15]. The BMI was derived and BMI Z-score was obtained using U.S. data tables[12]. Waist circumference (WC) was also measured by the same single observer and was measured in centimeters, using a non-stretch flexible tape measure, to the nearest 0.1 cm. The tape was placed above the iliac crest, parallel to the ground, with the individual standing with the abdomen relaxed, arms to the side, and feet together. The cut-off was taken as the 75th percentile or greater, according to age and ethnicity[16].

Body fat mass assessment

The two-compartment model of body composition was assessed by bioelectrical impedance analysis (BIA), using a standardized body composition analyzer (Biodynamics Corporation, Seattle, WA, USA). Measurements were performed in the morning, without performing any prior vigorous physical activity and before breakfast, after a 10 to 12-hour overnight fast. The procedure required subjects to be in the supine position. Fat free mass (FFM), Fat Mass (FM), and the percentage of body fat mass (%BF) were calculated using validated equations[17] and in accordance with National Institutes of Health guidelines[18].

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed on a treadmill (X-Fit 7 Power Treadmill), using protocols in accordance with age and progressive intensities. The ramp protocol was used, which consists of 8 to 12 minutes of exercise with small and constant increments in speed and gradient based on the expected maximum oxygen consumption[19]. Criteria for the maximum test were: a) exhaustion or inability to maintain the required speed, b) HR equal to or above 200 bpm, c) respiratory exchange ratio (RER) equal to or greater than one. VO_2max was determined

by the average of the three highest consecutive values obtained during the maximum test[20].

Oxygen consumption (VO_2), volume of expired carbon dioxide (VCO_2), and ventilation (VE) were measured in a gas analyzer using open-circuit ergospirometry (Parvo Medics TrueOne® 2400 Metabolic Measurement System, Sandy, UT, USA), and the respiratory exchange ratio (RER) was calculated.

Measurement of biochemical markers

Participants were instructed to visit the hospital after 12 hours of fasting. All visits occurred in the morning, before any vigorous physical activity. Blood samples were collected to obtain a hemogram and levels of glucose, insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triacylglycerol (TAG), human adiponectin, and C-reactive protein (CRP). Data were collected by venipuncture and the blood samples were stored in dry tubes for biochemical measurements. The colorimetric enzymatic method was used to measure TC, HDL-c, and TAG. The cutoff points were those proposed to Brazilian children and adolescents[21]. LDL-c was calculated using the Friedewald et al.[22] formula. The ultra-sensitive CRP was measured by the turbidimetric assay and adiponectin, by the ELISA method (Adiponectin DuoSet, R&D Systems, Inc., Minneapolis, MN, USA).

Intima-media thickness (IMT) assessment

The IMT of the common carotid artery (1-2 cm proximal to the carotid bifurcation) was assessed bilaterally in the posterior wall of the vessel with the aid of an ultrasound device (Philips SONOS 5500 with 8 MHz linear transduction). The procedure required subjects to be in the supine position and resting their back on a pillow. The average of three values of the right-side c-IMT (c-IMTr) and left-side c-IMT (c-IMTl) was retained for analysis. c-IMT corresponds to the mean of c-IMTr and c-IMTl. All measurements were performed by the same experienced observer (clinician at Hospital das Clínicas - UFPR). The intraobserver coefficient was 8% for c-IMTl and 2% for c-IMTr.

Statistical analysis

The initial analysis was descriptive in nature to determine the means and standard deviations for anthropometry, metabolic markers, and IMT. The normality of data was assessed by the Shapiro-Wilk test. When necessary, values were transformed into natural logarithm (*logn*) for normalization. As for the proportion and prevalence, we used the chi-square test and Fisher's exact test. The independent T test was used for parametric data and the Mann-Whitney U test was used for nonparametric data in order to compare variables between groups. Pearson's correlation for parametric data and Spearman's correlation for non-parametric data were used to analyze the possible relationship among BMI, VO_2max, inflammatory markers, lipid profile, and c-IMT. For proper analysis, the classification of the magnitude of the correlations was used: r=0.10 to 0.30 (weak), r=0.40 to 0.60 (moderate), r=0.70 to 1.0 (strong). The level of significance was p<0.05. Statistical tests were performed with the SPSS Statistics 18.0 software (SPSS Inc.).

Results

Fifty-three adolescents participated in this study and were divided into two groups according to the presence or absence of obesity. The sample consisted of 35 subjects in the obese group (19 boys and 16 girls) and 18 subjects in the non-obese group (9 boys and 9 girls).

The clinical and anthropometric characteristics are presented in Table 1. The mean age was similar between the obese (12.3±1.7 years) and non-obese subjects (12.7±1.4 years). The mean height values did

Table 1. Clinical and anthropometric variables of the obese and non-obese groups (n=53).

Variables	Obese (N=35)	Non-obese (N=18)	p=
Age(years)	12.3±1.7	12.7±1.4	0.418
Weight(kg)	75.7±20.4	46.3±8.3	0.001
Height(cm)	156.2±11.1	157.5±8.5	0.677
BMI(kg/m²)	30.6±5.8	18.6±2.2	0.001
BMIz	2.93±0.81	−0.06±0.73	0.001
WC(cm)	99.5±14.4	67±4.8	0.001
SBP(mmHg)ᐃ	112.3±14.6	102.2±4.4	0.005
DBP(mmHg)ᐃ	72.9±11.7	74±4.5	0.495
%Body fat	40.6±4.7	24.5±7.04	0.000
%FFM	59.1±4.5	76.1±6.6	0.000
VO₂max(ml/kg/m)	27.7±4.17	37.9±6.4	0.000

BMI: body mass index; BMIz: body mass index z-score; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; %Body fat: percentage of body fat; %FFM: percentage of free-fat mass; VO₂max: maximum volume of oxygen; ᐃvariables that did not show a normal distribution.

not differ between groups. The obese group showed higher values for weight, BMI, BMI Z-score, and WC than the non-obese group (p<0.001) as a result of the initial group allocation. The mean SBP was higher in the obese group than in the non-obese group (p<0.005) and DBP did not differ between groups. As for the maturation stage, the groups were similar (p<0.59).

For WC, all subjects in the obese group showed increased abdominal adiposity, with 29 subjects (93%) above the 90th percentile. None of the non-obese subjects showed adiposity above the 75th percentile. In the total sample, there were eight (15.7%) subjects with systolic hypertensive measurements and 17 (33.3%) with diastolic hypertensive measurements. The obese group had a higher frequency of hypertensive measures in SBP (8 vs. 0, χ^2=4.74; p<0.029). The frequencies of DBP were similar between groups. The mean values of FM, fat percentage (%Body Fat), fat-free mass (FFM), and percentage of fat-free mass (%FFM) were higher in the obese group than in the non-obese group (p<0.01). As for cardiorespiratory variables, the obese group had lower levels of VO_2max and higher levels of HR_{rest} than the non-obese group (p<0.001).

The obese group showed higher frequencies of VO_2max, lower than the expected for age and sex, than the non-obese group (34 vs. 14; p<0.006). In the non-obese group, three (22.3%) subjects had normal values of VO_2max, while none of the subjects in the obese group reached this classification.

The clinical and laboratory variables are presented in Table 2. The obese subjects showed higher TAG and insulin values and lower HDL values than the non-obese ones (p<0.001). The TC, LDL, and glycemia (GL) variables were similar between groups.

The obese subjects had a higher number of occurrences of high TAG (13 vs. 1, χ^2=7.50; p<0.007) and low HDL (18 vs. 0, χ^2=17.21; p<0.00) than the non-obese ones. TC (10 vs. 5, χ^2=0.12; p<0.733) and LDL (2 vs. 0, p<0.27) did not differ between groups. Figure 1 shows the distributions of percentage values of changes in lipid profiles of both groups. The obese subjects had higher CRP, c-IMTr, and c-IMT values than the non-obese subjects (p<0.05) and lower adiponectin values (p<0.001). c-IMTl values were similar between the two groups.

BMI showed a strong positive correlation with weight (r=0.93; p<0.01), WC (r=0.95; p<0.01), Fat Mass (FM) (r=0.95; p<0.01), and %Body Fat (r=0.87; p<0.01) and an inverse correlation with %FFM(r=–0.88; p<0.01) and VO_2max (r=–0.68;

**Table 2.** Clinical and laboratory variables of the obese and non-obese groups (n=53).

Variables	Obese (N=35)	Non-obese (N=18)	p=
TC (mg/dl)	161.9±37.5	161.8±17.5	0.637
HDL(mg/dl)	44.7±6.8	65.5±12.8	0.000
LDL(mg/dl)	88.4±30.6	83.5±19.2	0.95
TAG(mg/dl)	126.6±70.6	63.9±19.3	0.001
GL(mg/dl)	87.8±9.4	85.8±4.4	0.32
INS(µUI/ml)	16.9±13.3	4.12±2.3	0.001
HOMA-IR	3.45± 3.24	0.88±0.52	0.001
CRP$^\Delta$(mg/L)	3.43±3.03	1.26±0.74	0.005
Adiponectin(µg/ml)	4.65±1.85	7.17±2.21	0.001
c-IMTr(mm)	0.43±0.04	0.40±0.03	0.004
c-IMTl(mm)	0.43±0.05	0.41±0.03	0.072
c-IMT(mm)$^\Delta$	0.43±0.04	0.40±0.02	0.016

TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; TAG: triacylglycerides; GL: glycemia; INS: insulinemia; HOMA-IR: Homeostasis Metabolic Assessment; CRP: c-reactive protein; c-IMTr: right intima-media thickness; c-IMTl: left intima-media thickness; c-IMT: mean intima-media thickness; Δvariables that did not show a normal distribution.

p<0.01). It was also moderately and directly correlated with SBP(r=0.45; p<0.01), HRrest (r=0.42; p<0.01), TAG (r=0.42; p<0.01), GL (r=0.40; p<0.01), and insulin (r=0.44; p<0.01) and inversely correlated with FFM (r=0.65; p<0.01), adiponectin (r=–0.51; p<0.01), and HDL (r=0.61; p<0.01).

The three measures of c-IMT showed a moderate direct correlation with weight, WC, BMI, FM, %Body Fat, and FFM and an inverse correlation with %FFM and VO_2max. Figure 1 shows the correlation between VO_2max and c-IMT. Only c-IMTr and c-IMT were moderately correlated with the BMI Z-score. As for laboratory variables, c-IMTr showed a weak positive correlation with LDL and GL, and a negative correlation with HDL. It was also moderately correlated with CRP. For c-IMT, we found only a weak inverse correlation with HDL. For c-IMTl, we did not find any correlations with any of the evaluated clinical and laboratory variables.

Adiponectin showed a moderate inverse correlation with weight, WC, FM, %Body Fat, and FFM and a positive correlation with %FFM. It was weakly and directly correlated with VO_2max. As for CRP, we found a weak direct correlation with WC and %Body Fat and an inverse correlation with %FFM. CRP and VO_2max were moderately and inversely correlated. As for laboratory variables, adiponectin showed moderate inverse correlation with insulinemia (INS).
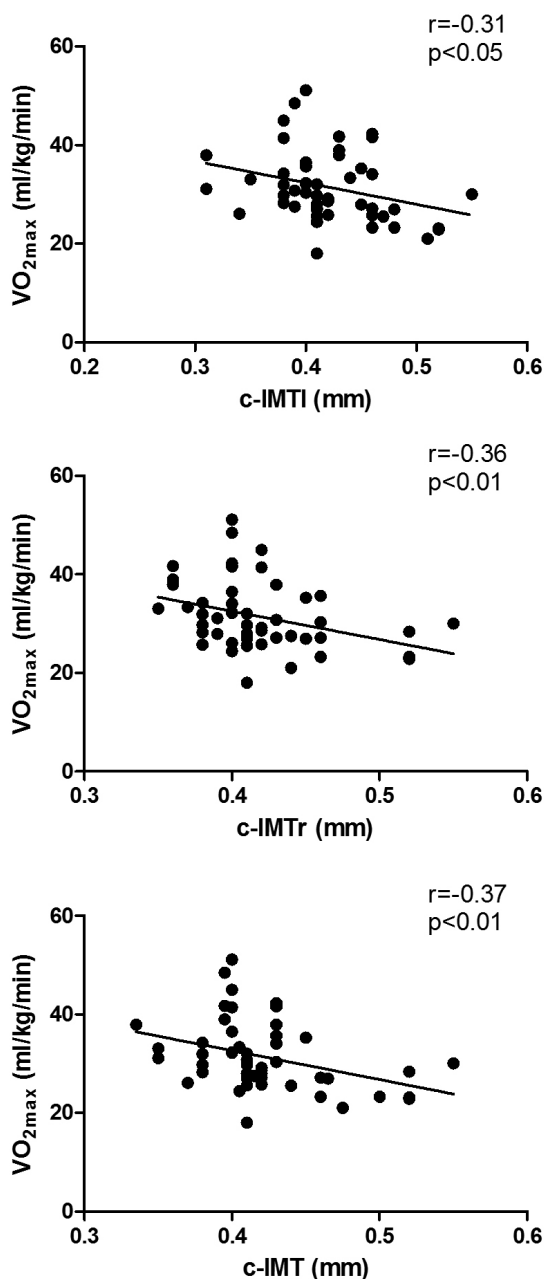
Figure 1. Correlation between maximal oxygen consumption (VO$_2$max) and left-side carotid intima-media thickness (c-IMTl), right-side carotid intima-media thickness (c-IMTr), and carotid intima-media thickness (c-IMT).

It was also weakly correlated with HDL and inversely correlated with TAG. CRP was moderately correlated with TAG and inversely correlated with HDL. Table 3 shows the correlations among the variables.

• **Discussion**

In our study, we found that obese children and adolescents presented higher c-IMT values than non-obese ones, corroborating previous studies that reported the contribution of obesity to the development of early atherosclerosis[23,24]. The risk factors for atherosclerosis, such as hypertension, dyslipidemia, diabetes, and insulin resistance, have been demonstrated in adults[25-28], however information on the association of c-IMT with different risk factors measured in childhood and adolescence is limited and contradictory. In a study conducted by Mangge et al.[29], BMI was positively correlated with c-IMT. Additionally, Beauloye et al.[4] found that SBP, insulin, and HOMA-IR were correlated with c-IMT. In contrast, some authors did not find any correlation between c-IMT and cardiovascular risk factors[3,30-32]. In the present study, we found that c-IMT was positively correlated with BMI, WC, %BF, and HOMA-IR and inversely correlated with HDL. These findings are in line with studies demonstrating that obesity, insulin resistance, and dyslipidemia can be associated with an increase in c-IMT in this population[33].

Recently, inflammation biomarkers have been considered a risk factor for early atherosclerosis[4,34,35]. Elevated PCR and reduced adiponectin levels are known to be more frequent in obese individuals[7]. We found that obese children and adolescents had higher PCR and lower adiponectin levels than non-obese ones. Also, we found that c-IMT was significantly correlated with PCR, but not with adiponectin. CRP is known to affect endothelial function via either direct or indirect mechanisms, such as reducing NO (nitric oxide) production and stimulating inflammation-oxidative stress pathways[34]. Moreover, adiponectin promotes the production of NO in endothelial cells, and hypoadiponectinaemia is associated with blunted endothelial function[30]. The lack of NO production induces vasoconstriction, leucocyte adherence, platelet activation, oxidative stress, and thrombosis, leading to endothelial dysfunction[34,36]. The lack of correlation between adiponectin and endothelial dysfunction in obese children and adolescents may be due to different signaling pathways in children and in adults, especially as regards phosphatidylinositol 3-kinase for adiponectin stimulation of NO production in endothelial cells[37]. In addition, the presence of multimetric forms of adiponectin and high-molecular-weight adiponectin is thought to be superior to total adiponectin level in predicting the c-IMT[37]. This was shown by Mangge et al.[31], who reported that only high-molecular-weight adiponectin was correlated with c-IMT in obese and non-obese children.

Table 3. Correlations between clinical, laboratory, and anthropometric variables.

Variables	c-IMTr	c-IMTl	c-IMT	Adipo	CRP
Weight(kg)	0.47**	0.44**	0.46**	−0.50**	0.29
WC(cm)	0.54**	0.43**	0.47**	−0.54**	0.38*
SBP(mmHg)Δ	0.09	0.28	0.24	−0.22	0.11
DBP(mmHg)Δ	0.24	0.10	0.23	0.08	−0.14
%Body fat	0.40**	0.30*	0.48**	−0.44**	0.35*
%FFM	−0.40**	−0.30*	−0.48**	0.44**	−0.35*
VO$_2$max(ml/kg/m)	−0.36**	−0.31*	−0.37**	0.37*	−0.42**
TC (mg/dl)	0.09	−0.01	0.04	−0.14	−0.07
HDL (mg/dl)	−0.32*	−0.25	−0.33*	0.35*	−0.40*
LDL (mg/dl)	0.13	−0.27	0.06	−0.75	−0.12
TAG (mg/dl)	0.26	0.07	0.21	−0.34*	0.38*
GL (mg/dl)	0.34*	0.27	0.27	0.08	0.11
INS(μUI/ml)	0.23	0.17	0.28	−0.59**	0.22
HOMA-IR	0.40**	0.23	0.34*	−0.55**	0.22
CRPΔ (mg/L)	0.40*	0.28	0.21	−0.03	---
ADIPO (μg/ml)	−0.14	−0.22	−0.17	---	−0.03

BMI: body mass index; BMIz: body mass index z-score; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; %Body fat: percentage of body fat; %FFM: percentage of free-fat mass; VO2max: maximum volume of oxygen; c-IMTr: right intima-media thickness; c-IMTl: left intima-media thickness; c-IMT: intima-media thickness mean; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TAG: triacylglycerides; GL: glycemia; INS: insulinemia; HOMA-IR: Homeostasis Metabolic Assessment; CRP: c-reactive protein; ADIPO: adiponectinemia; Δvariables analyzed using Spearman's correlation; *p<0.05; **p<0.01.

Our main finding was that cardiorespiratory fitness (VO$_2$max) was inversely associated with c-IMT. Studies have reported an inverse association between cardiorespiratory fitness and c-IMT in middle-aged[38,39] and elderly[39] individuals. In children and adolescents, only two studies investigated this relationship and the results were contradictory[40,41]. Kim et al.[40] found an inverse significant correlation between VO$_2$max and maximum IMT in Korean male adolescents. On the other hand, Pahkala et al.[41] did not find an association between fitness and c-IMT in Finnish adolescents. It is interesting to note that both studies estimated VO$_2$max using indirect methods. The gold-standard measure of cardiorespiratory fitness in humans involves direct assessment of peak or maximal oxygen consumption in response to an exercise test. We used the direct method to measure the VO$_2$max.

Cardiorespiratory fitness is strongly associated with reduced risk of cardiovascular disease and all-cause mortality[42]. There are several plausible mechanisms by which cardiorespiratory fitness might reduce the risk of carotid atherosclerotic vascular disease. Some studies suggest that the effect of exercise on arterial wall thickness is explained by exercise-mediated changes in traditional cardiovascular risk factors, such as adiposity, lipid levels, and blood pressure[39]. High levels of physical activity increase nitric oxide production, which improve vascular function by enhancing vasodilation and vasomotor function in the vessels. It also prevents platelet aggregation and adhesion in the endothelium, enhances fibrinolysis, improves lipid profiles, and reduces blood viscosity and fibrinogen levels, all of which may contribute to slowing the progression of carotid atherosclerotic vascular disease[39,43]. In contrast, other studies have demonstrated the impact of exercise on c-IMT regardless of changes in risk factors[39,43].

The strength of this study is that we assessed values directly by using gas analyzer and ramp protocol. A limitation of our study is that the number of patients was small and we did not analyze boys and girls separately. In order to minimize the possible effects of gender differences on our data, the number of boys and girls was proportional in both groups (around 50% in each group). Another limitation is that we used the HOMA-IR to assess insulin resistance, which is less accurate than hyperinsulinemic euglycemic clamp. Additionally, we did not measure other isoforms of adiponectin, which could be more

sensitive to correlation with c-IMT. Finally, the current study did not use a multivariable adjusted model.

The main finding of this study was the inverse correlation between c-IMT and VO$_2$max, which shows that low aerobic fitness in this age group can be a predictor of the development of increased c-IMT in childhood and adolescence. It also shows that regular physical activity may be a protective factor for atherosclerosis, regardless of the presence of other traditional cardiovascular risk factors and inflammation.

Conclusion

Obese children and adolescents had higher values of c-IMT, as well as metabolic and inflammatory profiles. c-IMT correlates not only with body composition, blood lipids, insulin resistance, and inflammation, but also with low VO$_2$max in children and adolescents. This result confirms the importance of regular physical activity to prevent cardiovascular disease. Further longitudinal studies are needed to determine whether the increase in cardiorespiratory fitness is associated with improvement in c-IMT during adolescence.

The authors declared no conflict of interest.

Acknowledgements

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