Original Article

Insulin Resistance Can Impair Reduction on Carotid Intima-Media Thickness in Obese Adolescents

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Abstract

Background: **The atherosclerotic process at the endothelial level begins in early ages and seems to be associated with obesity and its comorbidities as insulin resistance.**

Objective: **The aim of this study was to verify the influence of insulin resistance on inflammatory and subclinical markers of atherosclerosis in obese adolescents.**

Methods: **Sixty-six post-pubescent obese adolescents were divided in two groups according to homeostasis model assessment of insulin resistance (HOMA-IR) measurement: with insulin resistance (IR) n=39 and without insulin resistance (NIR) n=27, and submitted to an interdisciplinary intervention over the course of 1 year. Common carotid artery intima-media thickness (cIMT), visceral and subcutaneous adipose tissue was determined by ultrasound. Body composition, blood pressure, HOMA-IR, lipid profile and adipokines concentrations [leptin, adiponectin, and plasminogen activator inhibitor type (PAI-1)] were analyzed before and after the therapy.**

Results: **Both groups presented significant improvements in body composition, inflammatory state (reduction of leptin and PAI-1 concentration; increasing of plasma adiponectin) and reduction of cIMT. Only NIR group showed positive correlation between changes in visceral fat (ΔVisceral) and changes in cIMT (Δ cIMT) ($r = 0.42$; $p < 0.05$). Simple linear regression analyze revealed ΔVisceral to be an independent predictor to reduction of cIMT in this group (R2 adjusted = 0.14, $p = 0.04$). The final values of cIMT remained significantly higher in IR group when compared to NIR group.**

Conclusion: **The presence of insulin resistance can impair changes in cIMT leading to early development of atherosclerosis in obese adolescents submitted to an interdisciplinary intervention. (Arq Bras Cardiol 2012;99(4):892-898)**

Keywords: **Atherosclerosis; risk factors; obesity; adolescents; insulin resistance.**

Introduction

Carotid intima media thickness (cIMT) measurement is a marker of subclinical atherosclerosis and its increase has been associated with the presence of risk factors such as hypertension, dyslipidemia, diabetes, and obesity[1,2]. Some studies have shown that the atherosclerotic process at the endothelial level begins in early ages[3,4]. There are evidences that cIMT is higher in children with obesity than in healthy controls, and the effects of childhood obesity on the adult vasculature are cumulative[1,3,5].

Obesity is the most prevalent pathophysiological cause of insulin resistance (IR) that is defined as a decreased tissue response to insulin-mediated cellular actions, referring to whole-body reduced glucose uptake in response to physiological insulin concentration[6,7].

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Moreover, the adipose tissue, mainly the visceral fat, is related to an increase in cardiovascular risk and morbimortality besides producing several pro-inflammatory adipokines including leptin and plasminogen activator inhibitor type 1 (PAI-1) which play important regulatory functions in a variety of biological processes, including atherosclerosis, apart from their role in IR[6,8-12].

Studies involving different kinds of interventions (pharmacological, nutritional, lifestyle changes) have shown significant results in reducing cIMT in children and adolescents[13-16]. Previous study of our group demonstrated that the improvement of IR was an independent predictor to reduce cIMT in obese adolescents submitted to an interdisciplinary intervention over the course of 1 year[14]. However, the role of biomarkers associated with insulin resistance and obesity in both the development and treatment of subclinical atherosclerosis is not well elucidated.

Therefore, the aim of the present study was to verify whether the presence of insulin resistance exerts influence on response and association among inflammatory and subclinical markers of atherosclerosis in obese adolescents submitted to 1 year of interdisciplinary intervention.

Methods

Study subjects

A total of 66 post-pubescent[17] obese adolescents (BMI > 95th percentile on the CDC reference growth charts)[18], aged from 14 to 19 years (16.75 ± 1.63 years), including 39 with insulin resistance (IR) and 27 without insulin resistance (NIR), were recruited for an interdisciplinary weight loss program during 1 year. Hyperleptinemia was defined by leptin baseline values above 20 ng/ml for boys and 24 ng/ml for girls, as based on reference values cited by Gutin et al. (1999)[19]. The inclusion criteria for the post-pubertal stage were based on the Tanner scale (stage five) for both boys and girls. Non-inclusion criteria were as follows: other metabolic or endocrine diseases, chronic alcohol consumption, previous use of drugs such as anabolic-androgenic steroids or psychotropics, which may affect appetite regulation, and pregnancy. Informed parental consent and the adolescents' assent to participate as volunteer in an interdisciplinary weight loss program were obtained. This study was conducted in accordance with the principles of the Helsinki Declaration and was formally approved by the ethics committee of the Federal University of São Paulo (Number: 0135/04) and registered in the Clinical trial (NCT01357883).

Anthropometric measurements and body composition

Volunteers were weighed while wearing light clothing and no shoes on a Filizola scale to the nearest 0.1 kg. Height was measured to the nearest 0.5 cm with a wall-mounted stadiometer (Sanny, model ES 2030). Body mass index (BMI) was calculated as body weight divided by height squared (wt/ ht^2). Body composition was measured by air displacement plethysmography in a BOD POD body composition system (version 1.69; Life Measurement Instruments, Concord, CA).

Measurements of visceral and subcutaneous fat

All abdominal ultrasound procedures and measurements of visceral and subcutaneous fat were performed by the same blinded diagnostic imaging specialist using a 3.5 MHz multi-frequency transducer (broad band). This procedure allowed a reduction in the risk margin for misclassification. The intra-examination coefficient of variation for ultrasound was 0.8%. Ultrasound measurements of visceral and subcutaneous fat were taken. Ultrasound-determined subcutaneous fat was defined as the distance between the skin and external face of the rectus abdominis muscle, and visceral fat was defined as the distance between the internal face of the same muscle and the anterior wall of the aorta[20].

Measurements of carotid artery intima-media thickness

The carotid artery intima-media thickness was measured by the same experienced radiologist who was blinded to the participant's laboratory values and risk factor levels, before and after intervention, using high-resolution ultrasound equipment (Logic 5 and Logic 7, General Electric) with a 7-14 MHz linear array transducer. The intra-examination coefficient of variation for the cIMT was 4.36%. Patients were examined in the supine position with the neck in hyperextension. The protocol involved repeated manual measurements of the right and left common carotid far wall at 2 cm proximal to the bulb bifurcation. On a longitudinal B-mode image, the far wall of the common carotid artery appears as two bright parallel lines separated by a hypoechoic space. The distance between the leading edge of the first bright line on the far wall (lumen–intima interface) and the leading edge of the second bright line (media–adventitia interface) indicates the cIMT of the far wall as previously described[21]. Three measurements of the left and right common carotid were taken and the mean the higher measures of each side represented the cIMT in this study[2].

Serum analysis

Blood samples were collected at the outpatient clinic around 8 a.m. after

overnight fast. After collection, the blood was centrifuged for 10 min at 5,000 r.p.m. and stored at −70°C for future analyses. The materials used for collection were disposable, adequately labeled and of recognized quality. Blood was collected by a skilled and qualified technician.

Insulin resistance was assessed by the homeostasis model assessment-insulin resistance (HOMA-IR) index and the quantitative insulin sensitivity check index (QUICKI). HOMA-IR was calculated as the product of blood glucose (fasting blood glucose) and immunoreactive insulin (I): (fasting blood glucose (mg/dl) × I (mU/l)/405). QUICKI was calculated as 1/(log I + log FBG). The cutoff of HOMA-IR adopted for adolescents was 3.16[22].

The leptin, adiponectin and PAI-1 concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems (Minneapolis, USA), according to the manufacturer's instructions.

Blood pressure

Blood pressure (BP) was measured at least twice on the right arm using a mercury-gravity manometer with proper cuff size, with the volunteers in the seated position. The first appearance of sound (phase 1 Korotkoff sound) was used to define systolic BP, and the disappearance of sound (phase 5 Korotkoff sound) was used to define diastolic BP[14]. Hypertension was determined by reference values of BP percentiles for gender, according to age and height percentile[23].

Research design

The interdisciplinary weight loss program combined exercise training (aerobic plus resistance training) with clinical, nutritional and psychological therapy. All measurements were performed before and after one year of intervention.

Clinical therapy

To address the health and clinical parameters, obese adolescents visited the endocrinologist once each month. Medical follow-up and treatment were based on an initial patient and family history, physical examination and intervention in any health problems that had developed over the course of the therapy.

Exercise protocol

The combined exercise-training program was performed three times per week for 1 year and included 30 minutes of aerobic training plus 30 minutes of resistance training per session. The subjects were instructed to reverse the order of the exercises (aerobic and resistance) at each training session.

The aerobic training consisted of running on a motor-driven treadmill (Life Fitness–Model TR 9700HR) at a cardiac frequency intensity representing ventilatory threshold I (±4 bpm), according to the results of an initial oxygen uptake test for aerobic exercises. The exercise program was based on guidelines from the American College of Sports Medicine (ACSM), 2009[24].

Resistance training was also designed based on ACSM recommendations. Exercises targeted each of the main muscle groups. All adolescents had 2 weeks for adaptation to training to learn the movement (three sets of 15–20RM). After this introductory period, the load of training was adjusted and each eight weeks volume and intensity were adjusted inversely, decreasing the number of repetitions from 15-20 to 10-12 and 6-8 respectively, for three sets. All sessions were rigorously supervised by an experienced physiologist.

Nutritional therapy

Energy intake was set at levels recommended for subjects with low levels of physical activity of the same age and gender, following a balanced diet. Once a week, adolescents received dietetics lessons covering the topics related to a healthy eating pattern. All patients received individual nutritional consultation during the intervention program. At the beginning of the study and at 12 months into the program, a 3-day dietary record was collected. Because most obese people under-report their food consumption, each adolescent was asked to record their diet with help from their parents. The degree of under-reporting may still be substantial; however, this is a validated method for the assessment of dietary consumption[20]. These dietary data were transferred to a computer by the same dietician and the nutrient composition was analyzed by a PC program developed at the Federal University of São Paulo – Paulista Medicine School (Nutwin software, for Windows, version 1.5, 2002).

Psychological therapy

Psychological therapy treatment plans were established based on validated questionnaires taking into account some of the psychological problems caused by obesity, as described in the literature. These included depression, eating disorders, anxiety, decreased self-esteem, and body-image disorders. Interdisciplinary therapy consisted of a weekly 1 h group session. Individualized psychological therapy was recommended when weight problems were found.

Statistical analysis

Statistical analyses were performed using STATISTICA (version 7.0 for Windows). The Gaussian distribution of variables (including Δ values) was verified with a Kolmogorov Smirnov test. Variables with normal distribution were expressed as mean ± standard deviation (SD) while variables without normal distribution were expressed as median [quartile range] in a descriptive table. Analysis of variance for repeated measures (ANOVA) was used to compare the data from baseline and after therapy between the two groups for parametric variables, and Mann-Whitney U test followed by Wilcoxon signed rank, for non-parametric variables. Spearman correlation coefficients were calculated to assess possible relationships between non-normally distributed variables. Simple linear regression analysis was used to verify possible interrelationships between the measurements.

Results

Entire group

After 1 year of interdisciplinary intervention, both groups presented significant improvements in body composition (Table 1) [reduction of total body mass, body mass index (BMI), fat body mass (% and kg), visceral and subcutaneous fat and increasing lean body mass (%)]; lipid profile (Table 2) (reduction of total cholesterol, LDL-cholesterol and triglycerides); and inflammatory markers (Table 3) (reduction of leptin and PAI-1 concentration as well as increasing plasma adiponectin). Leptin/adiponectin ratio was also reduced (Table 3).

Both groups presented significant reduction in cIMT and increased in QUICKI values, as showed in Tables 3 and 2, respectively.

Non-insulin resistance group (NIR)

Significant reduction in visceral/subcutaneous fat ratio was observed at the end of weight loss therapy. After analyzing the correlation between ΔcIMT with changes (Δ) in body composition, lipid profile and inflammatory factors, a positive correlation was found only between Δ cIMT and changes in visceral fat (Δ visceral) ($r = 0.42$; $p < 0.05$). To identify possible cause-effect relationship in the correlation found, a simple linear regression analyze was performed and revealed that ΔVisceral to be an independent predictor to reduction of cIMT in this group (R^2 adjusted = 0.14, $p = 0.04$).

Insulin resistance group (IR)

At baseline conditions, this group presented positive correlation between cIMT and visceral/subcutaneous fat ratio ($r = 0.37$, $p < 0.05$), but the cIMT reduction did not associated itself with improvement of any variables.

Significant improvements in insulin concentration, HOMA-IR, VLDL and lean body mass (kg) were found after 1 year. Moreover, the final values of cIMT and QUICKI remained significantly higher and lower, respectively, in this group, when compared to NIR group.

Discussion

One of the most important finding of this study were significant reductions in hyperleptinemia, PAI-1, and leptin/adiponectin ratio, as well as an increase in adiponectin concentration (Table 3) in both groups. High PAI-1 concentration

Table 1 - Body composition in both groups before and after interdisciplinary intervention

	Without Insulin Resistance (NIR=27)									With Insulin Resistance (IR=39)								
	Baseline			1 Year			Δ			Baseline			1 Year			Δ		
Total Body Mass (kg)	99.70	±	12.95	89.68	±	12.61*	-10.02	±	6.35	110.95	±	15.90	98.88	±	17.22*	-12.08	±	8.62
BMI (kg/m^2)	36.33	±	4.78	32.39	±	4.76*	-3.94	±	2.52	38.46	±	5.21	33.84	±	5.58*	-4.62	±	3.13
Fat Body Mass (%)	47.38	±	5.77	39.94	±	7.86*	-7.44	±	4.27	47.85	±	5.55	38.39	±	7.52*	-9.47	±	4.60
Lean Body Mass (%)	52.62	±	5.77	60.07	±	7.85*	7.45	±	4.25	52.42	±	5.34	61.61	±	7.52*	9.28	±	4.51
Fat Body Mass (kg)	47.60	±	10.56	36.31	±	11.08*	-11.29	±	5.62	52.89	±	11.03	38.55	±	11.64*	-14.48	±	6.94
Lean Body Mass (kg)	52.09	±	6.28	53.23	±	6.03	0.60	±	[-0.70-4.40]	57.71	±	8.49	60.77	±	9.66*	1.30	±	[-0.12-6.40]
Visceral fat (cm)	4.13	±	1.12	2.41	±	1.00*	-1.66	±	0.77	4.71	±	1.64	3.23	±	1.36*	-1.51	±	1.41
Subcutaneous fat (cm)	4.12	±	0.96	3.09	±	0.64*	-0.97	±	0.97	4.14	±	0.89	3.36	±	0.86*	-0.82	±	0.77
Visc/Subc fat ratio	1.06	±	0.36	0.82	±	0.40*	-0.23	±	0.36	1.19	±	0.49	1.00	±	0.43	-0.18	±	0.46

Data expressed as mean ± SD and median [quartile range];
** Difference between baseline and after 1 year (p ≤ 0.05);*
p-value obtained by parametric test ANOVA for repeated measures
***BMI**-Body mass index*

Table 2 - Parameters related to lipid profile, glucose metabolism and blood pressure in both groups before and after interdisciplinary intervention

	Without Insulin Resistance (NIR=27)									With Insulin Resistance (IR=39)								
	Baseline			1 Year			Δ			Baseline			1 Year			Δ		
Total Cholesterol (mg/dL)	163	±	28	153	±	26 *	-9	±	12	166	±	32	155	±	26*	-11	±	19
LDL-c (mg/dL)	98	±	23	89	±	21*	-8	±	14	100	±	27	91	±	22*	-9	±	16
HDL-c(mg/dL)	46	±	10	48	±	10	2	±	4	43	±	8	44	±	7	1	±	6
VLDL (mg/dL)	18	±	8	15	±	7	-3	±	6	21	±	9	18	±	9*	-3	±	8
Triglycerides (mg/dL)	82	±	[58-113]	65	±	[52-79]*	-11	±	[-35-0]	95	±	[71-146]	76	±	[64-102]*	-15	±	[-38-5]
Glucose (mg/dL)	87	±	6	87	±	5	0	±	5	91	±	7	91	±	8	0	±	10
Insulin (iU/dL)	10.53	±	2.60	8.80	±	5.34	-3.10	±	[-4.20-0.87]	20.51	±	6.67	14.13	±	11.21*	-7.30	±	[-9.90--3.90]
HOMA-IR	2.26	±	0.53	1.93	±	1.25	-0.74	±	[-0.97-0.34]	4.64	±	1.62	3.30	±	3.29*	-1.61	±	[-2.60--0.69]
QUICKI	0.34	±	0.01	0.36	±	0.03*	0.02	±	0.03	0.31	±	0.01	0.33	±	0.03*†	0.02	±	0.03
MBP (mmHg)	129	±	[126-129]	83	±	[83- 86]*	-44	±	5	129	±	[126-132]	86	±	[83-93]*	-42	±	7

Data expressed as mean ± SD and median [quartile range];
** Difference between baseline and after 1 year (p≤0.05);*
† Difference between final values (p≤0.05);
p-value obtained by parametric test ANOVA for repeated measures and non-parametric test Mann-Whitney U test followed by Wilcoxon signed rank;
***LDL-c**-low-density lipoprotein-cholesterol; **HDL-c**-high-density lipoprotein-cholesterol; **VLDL**-very low-density lipoprotein; **HOMA-IR**-homeostasis model assessment insulin resistance index; **QUICKI**-quantitative insulin sensitivity check index; **MBP**-Mean Blood Pressure.*

is related to increased expression of cellular/vascular adhesion molecules and decreased insulin sensitivity, which are implicated in the initiation of endothelial dysfunction[25,26]. On the other hand, adiponectin exerts potent anti-inflammatory and anti-atherogenic role. Moreover, at the end of therapy there was reduction in the prevalence of hyperleptinemia in 36% (from 100% to 64%) associated to a reduction in 32% (from 59% to 27%) in insulin resistance in all analyzed patients (data not shown). The attenuation of inflammatory state promoted by this interdisciplinary therapy is relevant, once the altered concentration of these adipokines participates in the inception and progression of atherosclerosis[25,27].

In the NIR group, there was a significant reduction of visceral/subcutaneous fat ratio. This measure has being considered an important index of cardiovascular risk. Visceral fat is strongly associated with obesity-related complications like Type 2 diabetes and coronary artery disease[28,29].

Another relevant finding in the present investigation was the positive correlation between changes in visceral fat (ΔVisceral) and changes in cIMT (Δ cIMT) verified in this group. Studies have shown that the association between visceral adiposity and atherosclerosis development is independent of age, overall obesity or the amounts of subcutaneous fat. In addition, visceral

Table 3 - Inflammatory markers and carotid intima-media thickness (cIMT) in both groups before and after interdisciplinary intervention

	Without Insulin Resistance (NIR=27)			With Insulin Resistance (IR=39)		
	Baseline	1 Year	Δ	Baseline	1 Year	Δ
Leptin (ng/mL)	52.24 ± 24.74	30.36 ± 18.15*	-14.99 ± [-30.42--1.89]	51.66 ± 26.68	27.89 ± 19.95*	-18.32 ± [-27.71--6.51]
Adiponectin (ìg/L)	4.93 ± [3.72-9.89]	5.53 ± [4.07-10.39]*	1.19 ± 2.83	4.07 ± [3.11-7.49]	4.32 ± [3.72-9.44]*	1.39 ± 2.07
Leptin/Adiponectin ratio	10.45 ± [3.63-17.19]	3.76 ± [2.37-6.65]*	-3.08 ± [-10.11--0.94]	10.43 ± [4.83-19.14]	4.60 ± [2.12-7.19]*	-5.62 ± [-10.52--2.22]
PAI-1 (ng/mL)	12.69 ± 7.51	9.24 ± 8.31*	-3.70 ± 3.42	13.58 ± 8.17	9.11 ± 7.85*	-4.47 ± 7.18
Resistin (ng/mL)	14.94 ± 8.07	14.93 ± 7.08	-0.57 ± 3.48	15.84 ± 8.33	16.98 ± 9.11	0.63 ± 5.77
cIMT (mm)	0.40 ± 0.05	0.32 ± 0.04*	-0.07 ± 0.05	0.42 ± 0.06	0.37 ± 0.06*†	-0.05 ± 0.07

Data expressed as mean ± SD and median [quartile range];
** Difference between baseline and after 1 year (p ≤ 0.05);*
† Difference between final values (p ≤ 0.05);
p-value obtained by parametric test ANOVA for repeated measures and non-parametric test Mann-Whitney U test followed by Wilcoxon signed rank;
***PAI-1**=-plasminogen activator inhibitor 1; **cIMT**-carotid intima-media thickness.*

adipose tissue and its adipose-tissue resident macrophages present increased pro-inflammatory adipokines release and less adiponectin[28,29]. However, it is unclear how much visceral fat reduction is needed to induce favorable metabolic changes.

In this study, a mean reduction of 1.66 ± 0.77 cm in the visceral fat thickness presented a positive correlation with ΔcIMT in the NIR group, suggesting that insulin resistance could influence the association between visceral fat and cIMT, since this correlation was not found in the IR group. To better understand this association, simple regression analysis was performed. It was found that change in visceral fat was an independent predictor of improvement in cIMT, emphasizing the importance to develop strategies to avoid abdominal obesity and atherosclerotic disease[29]. These outcomes also suggest that the presence of IR could be contributed to positive correlation between cIMT and visceral/subcutaneous fat ratio.

Although both groups presented reduction on cIMT, it is important to observe that, in the IR group, this measure maintained significantly higher than in the NIR group, reinforcing that the frame of insulin resistance could corroborate the early development of atherosclerosis in obese adolescents.

One year of interdisciplinary therapy also promoted a significant improvement in body composition independently of the presence of insulin resistance (Table 1). These findings corroborate with literature evidences, that demonstrate the efficacy of weight loss programs in improving insulin sensitivity and avoiding that insulin resistance impair weight loss process in obese children and adolescents[30,31].

Conclusions

This study shows that the presence of insulin resistance seems influence on response and association among inflammatory and subclinical markers of atherosclerosis in obese adolescents submitted to an interdisciplinary intervention. Further studies are required to better comprehension of mechanisms involved in the association among obesity, insulin resistance and subclinical atherosclerosis, their early prevention and enhance clinical treatment.

Potential Conflict of Interest

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

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Study Association

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