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Original/*Pediatría*

Cut-off values of waist circumference to predict metabolic syndrome in obese adolescents

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Abstract

Introduction: **Metabolic syndrome (MetS) is a constellation of metabolic alterations related to abdominal obesity, inflammation and insulin resistance, which increase cardiovascular disease and mortality. The aims of the present study were to identify the prevalence of comorbidities and altered parameters in obese adolescents with and without MetS, and determine cut-off points of waist circumference to predict MetS.**

Methods: **195 obese adolescents were recruited and divided according to MetS diagnosis based on IDF criteria. Blood analyses of glucose, lipids, liver enzymes, adiponectin and leptin were measured. Insulin resistance was assessed by HOMA-IR, QUICKI and HOMA-AD. Visceral, subcutaneous and hepatic fat were ultrasonography obtained. Body composition was estimated by BOD POD system.**

Results: **We observed a prevalence of 25% of MetS (n=50). The MetS group presented significantly higher body mass, BMI, body fat (kg), free-fat mass (kg), waist circumference, visceral fat, glucose, insulin, insulin resistance, total-cholesterol, LDL-c, VLDL-c, triglycerides, liver enzymes, blood pressure and non-alcoholic fatty liver disease (NAFLD). Significant lower QUICKI and adiponectin were noted in MetS group. MetS girls presented significantly higher leptin/adiponectin ratio compared to Non-MetS girls. Cut-off points of 111.5 cm for boys and 104.6 cm for girls of waist circumference were suggested to predict metabolic syndrome. Moreover, waist circumference was positively correlated with visceral fat and the number of metabolic syndrome parameters.**

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LOS VALORES DE CORTE DE CIRCUNFERENCIA DE CINTURA PARA PREDECIR EL SÍNDROME METABÓLICO EN ADOLESCENTES OBESOS

Resumen

Introducción: **El síndrome metabólico es una constelación de alteraciones metabólicas relacionadas con la obesidad abdominal, la inflamación y la resistencia a la insulina, lo que aumenta las enfermedades cardiovasculares y la mortalidad. Los objetivos del presente estudio fueron determinar la prevalencia de comorbilidades y parámetros alterados en adolescentes obesos con y sin SM, y determinar los puntos de corte de la circunferencia de cintura para predecir SM.**

Métodos: **195 adolescentes obesos y se los dividió según síndrome metabólico diagnóstico basado en criterios de la IDF. Los análisis de sangre se midieron de glucosa, lípidos, enzimas hepáticas, la adiponectina y leptina. Resistencia a la insulina se evaluó mediante HOMA-IR, QUICKI y HOMA-AD. Se obtuvieron ecografía visceral, subcutánea y grasa hepática. La composición corporal se calcula por el sistema BOD POD.**

Resultados: **Se observó una prevalencia del 25% de síndrome metabólico Mets (n = 50). El grupo grupo con síndrome metabólico presentó mayor masa corporal, índice de masa corporal, grasa corporal (kg), sin grasa masa significativa (kg), circunferencia de la cintura, la grasa visceral, la glucosa, la insulina, resistencia a la insulina, colesterol total, LDL-c, VLDL-c, triglicéridos, enzimas hepáticas, enfermedad no alcohólica del hígado graso (EHNA) y la presión arterial. Se observaron QUICKI significativamente menor y la adiponectina en el grupo con síndrome metabólico. El grupo con síndrome metabólico presentaron significativa proporción de leptina / adiponectina mayor en comparación con los que no tienen síndrome metabólico. Puntos de corte de 111,5 cm para los niños y 104,6 cm para las niñas de la circunferencia de cintura se sugirieron para predecir el síndrome metabólico. Además, la circunferencia de la cintura fue positivamente correlacionada con la grasa visceral y el número de parámetros del síndrome metabólico.**

Conclusion: **MetS group presented significantly higher metabolic alterations and inflammation compared to Non-MetS group. Waist circumference is considered an anthropometric measure predictor of metabolic syndrome in obese adolescents, being useful in clinical practice.**

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Key words: *Metabolic syndrome. Cut off point. Waist circumference. Non-alcoholic fatty liver disease and inflammation.*

Conclusión: **El grupo con síndrome metabólico presentan alteraciones metabólicas significativas superiores e inflamación en comparación con el grupo sin síndrome metabólico. La circunferencia de cintura se considera un predictor medida antropométrica del síndrome metabólico en adolescentes obesos, siendo útil en la práctica clínica.**

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Palabras clave: *Síndrome metabólico. Cortaron punto. Circunferencia de la cintura. La enfermedad de hígado graso no alcohólico y la inflamación.*

Abbreviations

A/L ratio: Adiponectin/leptin ratio
ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
BMI: Body Mass Index
CDC: Center for Disease Control
DBP: Diastolic Blood Pressure
GGT: Gama Glutamil Transferase
HDL-c: High Density Lipoprotein-cholesterol
HOMA-AD: Homeostasis Model Assessment -Adiponectin
HOMA-IR: Homeostasis Model Assessment - Insulin Resistance
IDF: International Diabetes Federation
IL-6: Interleukin 6
L/A ratio: Leptin/adiponectin ratio
LDL-c: Low Density Lipoprotein-cholesterol
MBP: Mean Blood Pressure
MetS: Metabolic Syndrome
NAFLD: Non Alcoholic Fatty Liver Disease
PAI-1: Plasminogen Activator Inhibitor 1
QUICKI: Quantitative Insulin Sensitivity Check Index
SBP: Systolic Blood Pressure
TC: Total cholesterol
TG: Triglycerides
TNF-α: Tumor Necrosis Fator α
VLDL-c: Very Low Density Lipoprotein -cholesterol

Introduction

The prevalence of childhood obesity is increasing, and about 40 million preschool children worldwide were overweight or obese in 2010, which represents an increase of 60% in the last two decades[1]. The obesity in childhood is associated with risk factors related to cardiovascular disease later in life. In a population-based study, obesity during childhood was the strongest risk factor for metabolic syndrome (MetS)[2].

MetS is defined by a combination of alterations, including hyperlipidaemia, insulin resistance, hyperglycemia, hypertension and abdominal obesity, which consist in a constellation of an interconnected physiological, biochemical, clinical and metabolic factors. In this regard, MetS confers a 5-fold increase in the risk of type 2 diabetes mellitus and 2-fold the risk of developing cardiovascular disease over the next 5 to 10 years[3]. The presence of metabolic alterations in children and adolescents with obesity is remarkable, being necessary to be investigated and treated[4].

The abdominal fat is considered the key determinant of metabolic risk, since the pro-inflammatory adipokines secreted by visceral fat are related to increased blood pressure, dyslipidemia and insulin resistance[5-6]. In obese adolescents, high levels of pro-inflammatory adipokines and reduced levels of anti-inflammatory adipokines, such as, leptin and adiponectin respectively, are associated with metabolic disorders, such as, insulin resistance, high levels of glucose, dyslipidemia and elevated carotid intima media thickness[7-9]. In this way, abdominal fat accumulation can mediate the association between obesity and cardiovascular risks[10].

Atherogenic risk factors, fibrinolysis, oxidative stress and hypoadiponectinemia often cluster with MetS and cardiovascular risks[5]. Furthermore, hyperleptinemia has been related to cardiovascular risks and atherosclerosis process. Hyperleptinemic obese adolescents were unable to increase adiponectin concentration after weight loss, which suggests the role of hyperleptinemia in the impairment of the attenuation of inflammation and thus leading to a decrease in vascular protection[11]. On the other hand, hypoadiponectinemia is related to increase cardiovascular risks, such as metabolic syndrome, type 2 diabetes and atherosclerosis in obese patients[7-9].

Recently, non-alcoholic fatty liver disease (NAFLD) is considered an emerging public health concern that parallels rise in obesity and MetS. The relationship between NAFLD and the features of the MetS have been extensively reported, and waist circumference can also predict it[12].

Although children and adolescents with MetS present increased risk of cardiometabolic outcomes during adulthood, they are not destined for a lifetime of increased risk if they treat the MetS status early in life[13]. Reports from the Young Finns Study cohort demonstrated that after 6 year, the subjects that recovery MetS had beneficial impact on preclinical atherosclerosis estimated by carotid intima media thickness when compared to those who had persistent MetS diagnoses,

indicating the importance of diagnoses and treatment of MetS for preventing atherosclerosis process and future cardiac events[14].

Although defined as an indirect method, waist circumference is considered an important measure correlated with visceral fat accumulation, including in obese adolescents[15]. Data from the Bogolusa Heart Study showed a high cardiometabolic risk among normal and overweight children with abdominal obesity compared to overweight children without excessive abdominal fat accumulation[16].

In this way, waist circumference need to be considered in clinical practice in order to estimate the risks of abdominal fat accumulation and as a predictor of cardiometabolic risks, such as, MetS. The data mentioned above reinforce the importance of the definition of reference values of waist circumference for the prognostic of MetS to improve obesity comorbidities. Therefore, the first aim of the present study was to identify the prevalence of comorbidities and altered parameters in obese adolescents with and without MetS. The second objective was to determine cut-off points of waist circumference to predict MetS in obese adolescents of both genders.

Methods

Subjects

This cross-sectional study involved 195 obese adolescents aged from 15 to 19 years. All participants met the inclusion criteria of post-pubertal Tanner Stage ≥ V and a body mass index (BMI) >95th percentile of CDC. Endocrinologist completed a clinical interview to determine inclusion and exclusion criteria. Exclusion criteria included identified genetic, previous drug utilization, chronic alcohol consumption (≥20 g/d), presence of viral hepatic diseases, and other causes of liver steatosis.

This study was conducted according to the principles laid down in the Declaration of Helsinki, was approved by Institutional Ethical Committee (72538) of Universidade Federal de São Paulo, and was registered with ClinicalTrials.gov (NCT01358773). Informed consent was obtained from all participants and/or their parents.

Anthropometric measurements and body composition

Volunteers were weighed while wearing light clothing and barefoot on a Filizola scale to the nearest 0.1 kg. Height was assessed using a stadiometer with a precision of 0.1 cm (Sanny, São Bernardo do Campo, SP, Brazil; model ES 2030). BMI was calculated as body weight divided by height squared (wt/ht^2). For the determination of waist circumference, subjects were placed in a standing position with the abdomen and arms relaxed alongside the body, and a flexible measuring tape (1mm accuracy) was held horizontally at the midpoint between the bottom edge of the last rib and the iliac crest. Body composition was estimated by Plethysmography Air Displacement in the BOD POD system (version 1.69, Life Measurement Instruments, Concord, CA, USA).

Visceral and subcutaneous adiposity, and Hepatic Steatosis

Visceral and subcutaneous fat were estimated by abdominal ultrasonography by one physician blinded to subject assignment groups. Subcutaneous fat was defined as the distance between the skin and superficial plane of the rectus abdominal muscle. Visceral fat was defined as the distance between the deep plane of the same muscle and the anterior wall of the aorta[17]. Steatosis evaluation was performed based on criteria reported earlier[8].

Blood Pressure

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the right arm using a mercury-gravity manometer with appropriate cuff size. Mean blood pressure (MBP) was calculated as DBP+[(SBP−DBP)/3].

Serum analysis

Blood samples were collected after a 12-hour overnight fast. Concentrations of glucose, insulin, triglycerides (TG), total cholesterol (TC), high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c), very low density lipoprotein-cholesterol (VLDL-c) and hepatic transaminases [alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gama glutamil transferase (GGT)] were determined by enzymatic colorimetric methods (CELM, Barueri, Brasil). The ratios of lipoproteins levels (TC/HDL-c, LDL-c/HDL-c, and TG/HDL-c) were also calculated.

Leptin and adiponectin were measured by enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems (Minneapolis, MN, USA). For this study, leptin data was analyzed according to reference values[18]. The pro-inflammatory leptin/ adiponectin ratio (L/A ratio) and anti-inflammatory adiponectin/ leptin ratio (A/L ratio) biomarkers were calculated.

Insulin resistance was determined by the Homeostasis Model Assessment Insulin Resistance (HOMA-IR): [Fasting insulin (μU/mL) x fasting blood glucose (mmol/L)/22.5][19]. Insulin sensitivity was determined by the Quantitative Insulin Sensitivity Check Index (QUICKI): [1/ (log fasting insulin (μU/mL) + log fasting glucose (mg/dL)][20]. Homeostasis Model Assessment-Adiponectin (HOMA-AD) was calculated from fasting blood glucose, insulin and adiponectin: [fasting glucose (mg/dl) x fasting insulin (μU/L)/Adiponectin (μg/mL)][21]. The cutoff of HOMA-IR adopted for adolescents was 3.16[22] and insulin was 15.0[23].

Metabolic syndrome diagnosis

Metabolic syndrome diagnoses were made when waist circumference was higher than the 90th percentile for age and gender and associated with two or more criteria of IDF[24]: HDL-c values ≤50 mg/dL for girls and ≤40 mg/dL for boys; concentrations of TG higher than 150 mg/dL; blood glucose levels higher than 100 mg/dL, and blood pressure ≥130/85 mmHg. Patients were distributed into two groups, with metabolic (MetS) and without MetS (Non-MetS). The number of metabolic alterations was obtained according to these parameters.

Statistical analysis

Statistical analyses were performed using PASW Statistics version 20 (SPSS Inc., Chicago, IL, USA) with the level of statistical significance set at $p < 0.05$. The distributional assumptions were verified by Kolmogorov–Smirnov test. Parametric variables were expressed as means±standard deviation, whereas non-parametric variables were expressed as medians (minimum–maximum). Comparisons between MetS group and Non-MetS, and according to gender, were made using independent t tests for parametric variables and the Mann Whitney test for non-parametric variables. Pearson and Spearman correlations were performed to test the direction and strength of the relationship between the variables of the study. Logistic regression analysis was employed to determine which factors were predictor variables of MetS. Chi-square test was used to verify the association between prevalence of categorical variables between MetS and Non-MetS groups.

A receiver operating characteristic (ROC) curve was constructed in order to establish waist circumference cut-off points for obese boys and girls that could be used to predict MetS. Sensitivity was defined as the probability of waist circumference to classify correctly those subjects presenting MetS (true positives), whereas specificity was defined as the probability of waist circumference to classify correctly those subjects presenting non-MetS (true negatives). The area under the ROC curve was employed as a global measure of the general precision of waist circumference as a predictor of MetS, in which an area of 1 would correspond to 100% sensitivity and 100% specificity and, thus, represent a perfect test for discriminating individuals. The shortest distance in the ROC curve was calculated using the function: $\sqrt{(1 - \text{sensitivity}^2) + (1 - \text{specificity}^2)}$.

Results

Comparison between entire group with MetS and Non-MetS

The entire MetS group (boys + girls) presented significantly higher values of body mass, BMI, body fat (kg), fat-free mass (kg), waist circumference and visceral fat (Table I). In relation to metabolic variables, MetS group presented significantly higher values of

Table I
Antropometric and body composition profile of obese adolescents with and without metabolic syndrome

	Non-MetS			*MetS*		
	Entire group (n=145)	*Male (n=46)*	*Female (n=99)*	*Entire group (n=50)*	*Male (n=33)*	*Female (n=17)*
Age (years)	16.49 ± 1.45	16.31 ± 1.17	16.58 ± 1.56	16.56 ± 1.63	16.18 ± 1.57	17.28 ± 1.54
Body mass (kg)	97.22 ± 15.45	104.66 ± 14.80	93.76 ±14.56c	109.95 ± 14.40a	112.07 ± 15.68b	105.83 ± 10.78b
Height (m)	1.66 ± 0.09	1.74 ± 0.08	1.63 ± 0.06c	1.70 ± 0.08a	1.73 ± 0.08	1.64 ± 0.06c
BMI (kg/m^2)	35.01 ± 4.34	34.50 ± 4.10	35.25 ± 4.45	38.04 ± 4.81a	37.29 ± 4.83b	39.49 ± 4.55b
Body fat (%)	43.45 ± 7.06	38.46 ± 7.11	45.77 ± 5.73c	44.42 ± 6.35	42.44 ± 6.04b	48.25 ± 5.20c
Fat-free mass (%)	56.55 ± 7.07	61.56 ± 7.14	54.23 ± 5.73c	55.58 ± 6.35	57.56 ± 6.04b	51.75 ± 5.20c
Body fat (kg)	42.59 ± 11.28	40.72 ± 11.36	43.46 ± 11.20	49.19 ± 11.18a	48.04 ± 11.81b	51.41 ± 9.78b
Fat-free mass (kg)	54.64 ± 9.30	63.99 ± 8.57	50.30 ± 5.76c	60.76 ± 8.18a	64.04 ± 7.79	54.39 ± 4.31b,c
Waist circumference (cm)	97.73 ± 9.74	100.97 ± 8.12	96.23 ± 10.09c	108.74 ± 10.02a	109.38 ± 9.99b	107.51 ± 10.27b
Visceral fat (cm)	4.37 ± 1.32	4.95 ± 1.32	4.10 ± 1.24c	5.16 ± 1.59a	5.49 ± 1.67	4.53 ± 1.25c
Subcutaneous fat (cm)	3.82 ± 0.93	3.47 ± 0.76	3.98 ± 0.96c	3.98 ± 0.74	3.82 ± 0.72b	4.29 ± 0.69c
Visceral/subcutaneous fat	1.21 ± 0.46	1.48 ± 0.46	1.08 ± 0.40c	1.34 ± 0.47	1.47 ± 0.45	1.10 ± 0.42c

a Comparison between MetS x Non-MetS groups, $p<0.05$.
b Comparison between MetS x Non-MetS by gender, $p<0.05$.
c Comparison between Female x Male in the same group, $p<0.05$.

glucose, insulin, HOMA-IR, total-cholesterol, LDL-c, VLDL-c, TG, ALT, AST, GGT, SBP, DBP, MBP, TC/HDL-c, LDL-c/HDL-c, TG/HDL-c ratios and HOMA-AD (Table II). Significant lower values of QUICKI, HDL-c and adiponectin were also noted in MetS group (Table II).

Comparison between boys with MetS x Non-MetS

The MetS group presented significantly higher values of body mass, BMI, body fat (% and kg), waist circumference and subcutaneous fat (Table I). In relation to metabolic variables, MetS group presented significantly higher insulin, HOMA-IR, total-cholesterol, LDL-c, VLDL-c, TG, ALT, AST, SBP, DBP, MBP, TC/HDL-c, LDL-c/HDL-c, TG/HDL-c ratios and HOMA-AD (Table II). Significant lower values of fat-free mass (%), HDL-c and QUICKI were observed in MetS compared to Non-MetS (Table I and II).

Comparison between girls with MetS x Non-MetS

The MetS group presented significantly higher values of body mass, BMI, body fat (kg), fat-free mass (kg) and waist circumference (Table I). In relation to metabolic variables, MetS group presented significantly higher insulin, HOMA-IR, VLDL-c, TG, SBP, DBP, MBP, TC/HDL-c and TG/HDL-c ratios. Significant lower values of QUICKI and HDL-c were observed in MetS compared to Non-MetS girls. MetS group also presented significantly higher leptin/adiponectin ratio and HOMA-AD, and lower adiponectin than Non-MetS group (Table II).

Comparison between gender at same group

Comparing boys and girls with MetS, boys presented significantly higher values of height, fat-free mass (% and kg), visceral fat and visceral/ subcutaneous fat compared to girls. On the other hand, girls presented significantly higher values of body fat (%) and subcutaneous fat (Table I). In relation to metabolic parameters, significant higher values of LDL-c, AST, ALT, GGT, TC/HDL-c, LDL-c/HDL-c and TG/HDL-c ratios were observed in boys with MetS. HDL-c was significantly higher in girls compared to boys (Table II).

Analyzing Non-MetS boys and girls, we observed that boys presented significantly higher body mass, height, fat-free mass (% and kg), waist circumference, visceral fat and visceral/subcutaneous fat. Significant higher values of body fat (%) and subcutaneous fat were observed in girls (Table I). Glucose, AST, ALT, GGT, DBP, MBP and TG/HDL-c ratio were significantly higher, and HDL-c was significantly lower in boys compared to girls. Leptin was also significantly higher in girls (Table II).

Prevalence of metabolic syndrome parameters, hyperleptinemia and NALFD

Figure 1 illustrates the prevalence of altered parameters of MetS, hyperinsulinemia, hyperleptinemia and NALFD in the entire group (a), in boys (b) and girls (c) with and without MetS. In the entire group, significantly higher prevalence of altered waist circumference, glucose, HLD-c, TG, SBP, DBP, hyperinsulinemia, insulin resistance and NAFLD were observed in MetS compared to Non-MetS individuals. Similar results were noted in the analysis according to gender, in boys and girls (Figure 1b and c). Only in boys, there was no significant difference in the prevalence of high blood glucose between MetS and Non-MetS patients.

Correlations of waist circumference

Waist circumference was positively correlated with body mass ($r=0.77$, $p=0.00$), BMI ($r=0.71$, $p=0.00$), body fat (%) ($r=0.36$, $p=0.00$), body fat (kg) ($r=0.69$, $p=0.00$), visceral fat ($r=0.49$, $p=0.00$), subcutaneous fat ($r=0.34$, $p=0.00$), insulin ($r=0.43$, $p<0.05$), HOMA-IR ($r=0.44$, $p<0.05$), ALT ($r=0.31$, $p<0.05$), AST ($r=0.23$, $p<0.05$), GGT ($r=0.27$, $p<0.05$), SBP ($r=0.34$, $p<0.05$), DBP ($r=0.40$, $p<0.05$), MBP ($r=0.40$, $p<0.05$), leptin/adiponectin ratio ($r=0.28$, $p<0.05$) and HOMA-AD ($r=0.40$, $p<0.05$). Negative correlations between waist circumference and QUICKI ($r=-0.46$, $p<0.00$), adiponectin ($r=-0.24$, $p<0.05$) and adiponectin/leptin ratio ($r=-0.27$, $p<0.05$) were also observed. Interestingly, waist circumference was positively correlated with the number of MetS parameters ($r=0.57$, $p=0.00$).

Logistic Regression Analysis

In the logistic regression analysis, using the diagnosis of MetS as a dependent variable, it was found that body mass, BMI, body fat (%), visceral fat, waist circumference, insulin, HOMA-IR, total cholesterol, HLD-c, LDL-c, VLDL-c, triglycerides, SBP, DBP and adiponectin concentration were predictors to development of MetS (Table III). In the analysis adjusted by age and gender, waist circumference and age were together associated with MetS diagnosis (Table III).

Cut-Off point of waist circumference for metabolic syndrome

Analysis of the ROC curves revealed cut-off points of 111.5 cm for boys and 104.6 cm for girls (Figure 2). The area under the ROC curve for the girls group was 0.792 ($p = 0.001$) and that for boys group was 0.733 ($p = 0.000$).

Table II
Biochemical, blood pressure and inflammatory profile of obese adolescents with and without metabolic syndrome

	Non-MetS			*MetS*		
	Entire group (n=145)	*Male (n=46)*	*Female (n=99)*	*Entire group (n=50)*	*Male (n=33)*	*Female (n=17)*
Glucose (mg/dl)	90.50 ± 6.64	92.33 ± 7.36	89.65 ± 6.13c	92.88 ± 7.21a	93.67 ± 6.75	91.35 ± 8.02
Insulin (Uu/ml)	13.86 (3.98 - 32.44)	14.60 (7.44 - 32.44)	13.30 (3.98 - 30.30)	18.43 (7.10 - 60.30)a	18.56 (8.30 - 60.30)b	18.30 (7.10 - 35.80)b
HOMA-IR	3.02 (0.85 - 7.52)	3.38 (1.58 - 7.52)	2.85 (0.85 - 7.10)	4.29 (1.45 - 16.07)a	4.26 (1.86 - 16.07)b	4.36 (1.45 - 7.77)b
QUICKI	0.325 ± 0.020	0.324 ± 0.017	0.326 ± 0.021	0.309 ± 0.020a	0.308 ± 0.021b	0.310 ± 0.017b
Total cholesterol (mg/dl)	161.51 ± 30.99	157.47 ± 35.89	163.39 ± 28.43	179.76 ± 29.93a	184.48 ± 32.42b	170.59 ± 22.51
HDL-c (mg/dl)	47.44 ± 9.49	43.84 ± 8.46	49.11 ± 9.51c	40.62 ± 8.37a	38.76 ± 7.95b	44.24 ± 8.19b, c
LDL-c (mg/dl)	96.41 ± 27.63	94.80 ± 31.94	97.16 ± 25.53	109.65 ± 26.07a	115.25 ± 28.19b	99.12 ± 17.84c
VLDL-c (mg/dl)	16 (7 - 187)	17.5 (7 - 187)	16 (7 - 45)	30 (11 - 54)a	30 (15 - 54)b	31 (11 - 46)b
Triglycerides (mg/dl)	82 (35 - 226)	85 (35 - 202)	80 (35 - 226)	151.5 (55 - 529)a	151 (74 - 529)b	154 (55 - 229)b
AST (U/l)	22 (10 - 60)	24 (15 - 60)	20 (10 - 52)c	25 (15 - 73)a	26.5 (19 - 73)b	20 (15 - 29)c
ALT (U/l)	21 (3 - 146)	27 (3 - 146)	20 (9 - 61)c	27 (12 - 112)a	35.5 (17 - 112)b	22 (12 - 39)c
GGT (U/l)	20 (7 - 155)	26.5 (10 - 155)	18 (7 - 56)c	25 (9 - 89)a	30 (15 - 89)	19 (9 - 41)c
SBP (mmHg)	120 (100 - 190)	120 (100 - 150)	120 (100 - 190)	130 (105 - 150)a	130 (105 - 150)b	130 (110 - 150)b
DBP (mmHg)	80 (65 - 110)	80 (65 - 90)	75 (65 - 110)c	80 (70 - 100)a	80 (70 - 100)b	80 (70 - 100)b
MBP (mmHg)	90 (76.67 - 136.67)	93.33 (76.67 - 110)	90 (80 - 136.67)c	96.67 (83.33 - 113.33)a	96.67 (85 - 113.33)b	96.67 (83.33 - 113.33)b
TC/HDL-c ratio	3.41 (1.72 - 6.97)	3.48 (2.00 - 6.43)	3.32 (1.72 - 6.97)	4.55 (2.69 - 6.67)a	5.17 (2.69 - 6.67)b	3.55 (2.96 - 5.62)b,c
LDL-c/HDL-c ratio	2.02 (0.60 - 4.43)	2.07 (0.72 - 4.43)	1.98 (0.60 - 4.41)	2.75 (1.42 - 4.80)a	3.07 (1.42 - 4.80)b	2.13 (1.44 - 3.28)c
TG/HDL-c ratio	1.70 (0.58 - 7.79)	2.14 (0.65 - 5.05)	1.66 (0.58 - 7.79)c	3.70 (1.17 - 12.60)a	4.40 (1.34 - 12.60)b	2.37 (1.17 - 6.06)b, c
Adiponectin (ug/l)	9.93 (0.26 - 97.17)	8.51 (2.01 - 42.71)	10.14 (0.26 - 97.17)	7.38 (1.83 - 33.46)a	7.80 (1.87 - 33.46)	5.33 (1.83 - 12.93)b
Leptin (ng/ml)	30.50 (1.69 100.00)	21.52 (1.69 – 80.36)	34.51 (2.73 - 100)c	25.33 (1.24 - 97.44)	21.36 (1.24 - 97.44)	40.08 (4.07 - 96.67)
Leptin/Adiponectin ratio	2.00 (0.19 - 38.93)	1.95 (0.22 - 22.17)	2.16 (0.19 - 38.93)	3.27 (0.15 - 31.11)	2.37 (0.15 - 31.11)	4.27 (0.77 - 25.88)b
Adiponectin/ Leptin ratio	0.50 (0.00 - 5.32)	0.51 (0.05 - 4.58)	0.47 (0.00 - 5.32)	0.33 (0.03 - 6.53)	0.42 (0.03 - 6.53)	0.26 (0.04 - 1.30)
HOMA-AD	7.34 (0.27 - 361.55)	7.82 (0.94 - 58.20)	6.75 (0.27 - 361.55)	13.90 (2.90 - 183.76)a	12.87 (2.90 - 183.76)b	14.99 (3.30 - 51.13)b

a Comparison between MetS x Non-MetS groups, p<0.05;
b Comparison between MetS x Non-MetS by gender, p<0.05;
c Comparison between Female x Male in the same group, p<0.05

Discussion

The findings of the present study demonstrated significantly higher prevalence of altered waist circumference, blood glucose, HDL-c, triglycerides and blood pressure in MetS than Non-MetS obese adolescents. Obese adolescents with MetS also presented significantly higher body mass, BMI, body fat, waist circumference, visceral fat, glucose, insulin, HOMA-IR, TC, LDL-c, VLDL-c, TG, blood pressure, Castell indices (TC/HDL-c, LDL-c/HDL-c and TG/HDL-c) and HOMA-AD, as well as, significantly lower QUICKI (Table I and II). These results elucidate the higher cardio metabolic alterations observed in MetS patients, which potentiate cardiovascular risks and atherosclerosis process. Therefore, low cost diagnosis is preventive and easy to apply in the development countries.

In the current preventive cardiology guidelines, it is strongly recommended the identification of MetS in clinical practice, once metabolic dysfunction adversely increases cardiovascular disease[24-25]. In a long-term epidemiologic study, subjects with MetS showed significantly higher alterations in ventricle, end-diastolic posterior wall thickness, septal wall thickness, relative wall thickness, and ventricle end-diastolic diameter than subjects without MetS[26].

In adolescents, the carotid intima media thickness, considered a subclinical marker of atherosclerosis, was positively correlated with MetS parameters, such as HOMA-IR, LDL-c, VLDL-c, low HDL-c, triglyceri-

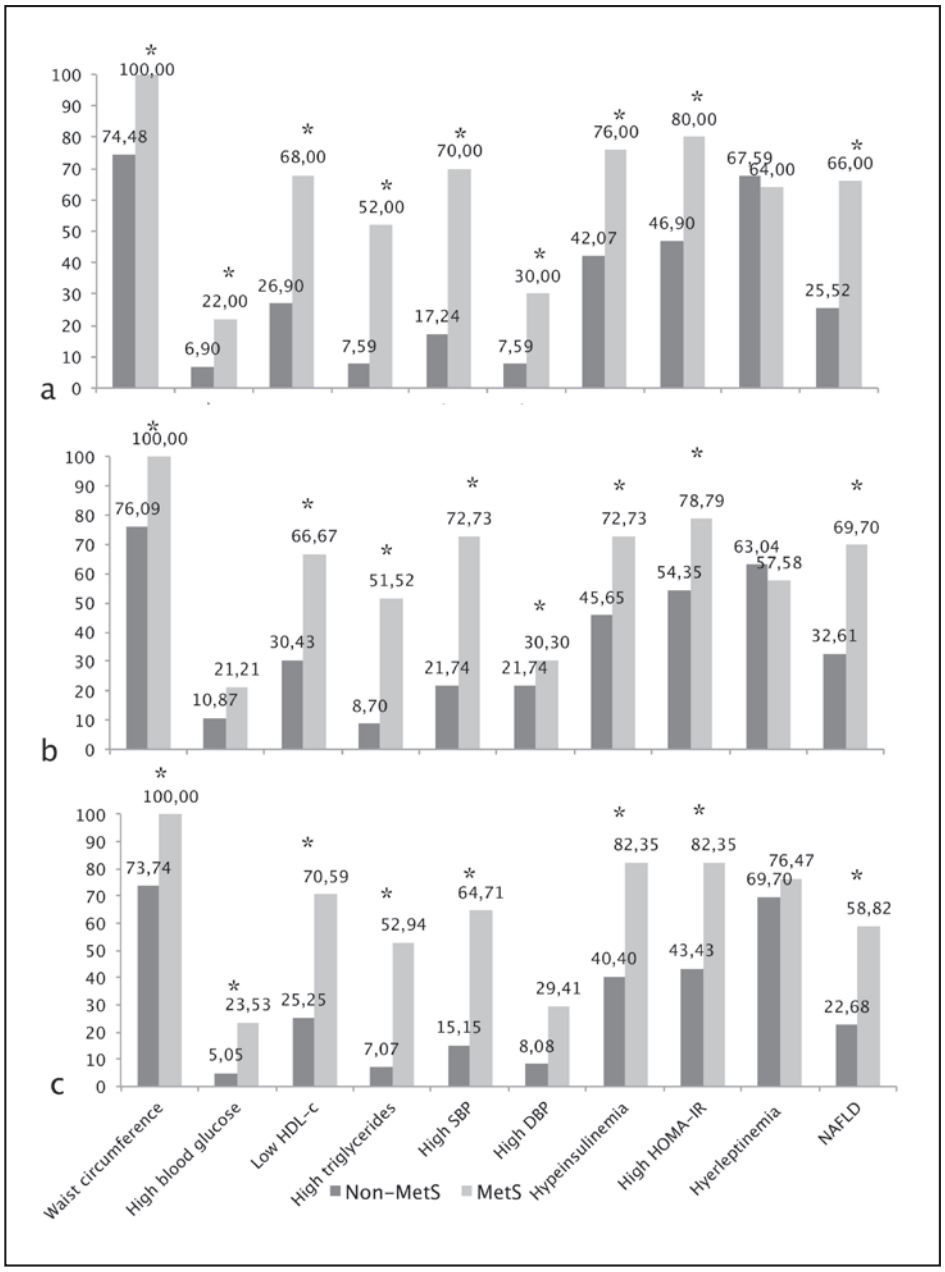

Fig. 1.—Prevalence of metabolic syndrome alterations, hyperisulinemia, insulin resistance, hyperleptinema, and non-alcoholic fatty liver disease in all obese adolescents (a), boys (b) and girls (c) with and without metabolic syndrome.

Table III.
Logistic regression for the determinants of metabolic syndrome.

	Metabolic syndrome			
	OR	*p*	*-95,00%*	*+95,00%*
Age	1.1	0.49	0.84	1.43
Gender	0.32	0.01	0.15	0.70
Waist circumference	1.11	0.00	1.06	1.16
Body mass	1.05	0.00	1.03	1.08
BMI	1.15	0.00	1.07	1.23
Body fat (%)	1.05	0.01	1.02	1.08
Visceral fat (cm)	1.46	0.00	1.16	1.85
Waist circumference	1.12	0.00	1.08	1.16
Insulin	1.12	0.00	1.06	1.18
HOMA-IR	1.67	0.00	1.32	2.11
Total-cholesterol	1.02	0.00	1.01	1.03
HDL-c	0.91	0.00	0.88	0.95
LDL-c	1.02	0.01	1.01	1.03
VLDL-c	1,10	0,01	1,03	1,18
Triglycerides	1.03	0.00	1.02	1.04
SBP	1.07	0.00	1.04	1.10
DBP	1.12	0.00	1.06	1.19
Adiponectin	0.92	0.01	0.89	0.98
Leptin	0.99	0.48	0.98	1.01
Leptin/Adiponectin ratio	1.02	0.28	0.98	1.07
Adiponectin/Leptin ratio	0.83	0.41	0.53	1.30
HOMA-AD	1.01	0.15	0.99	1.02

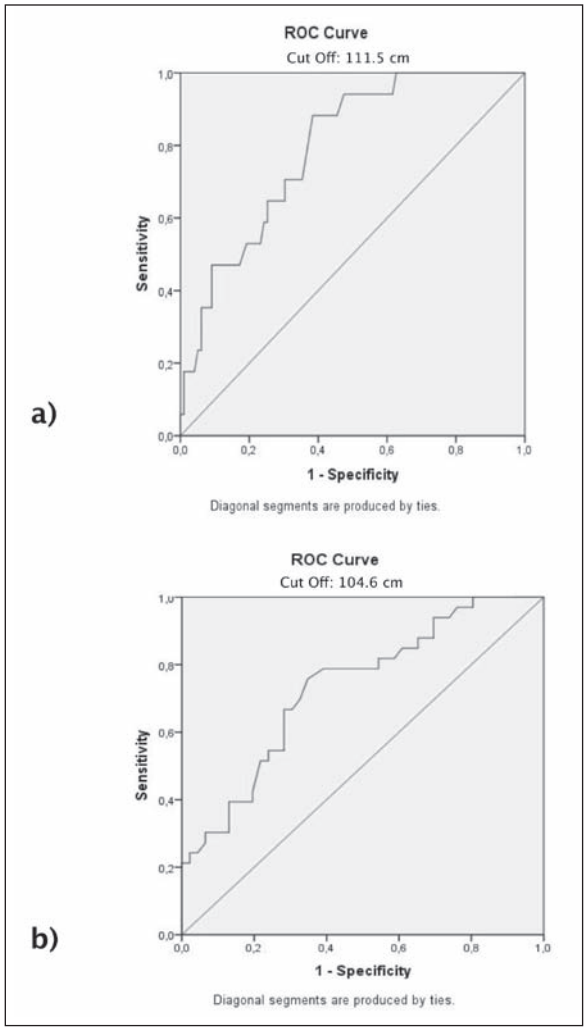

Fig. 2.—ROC curve for cut off point of waist circumference for metabolic syndrome diagnoses in boys (a) and girls (b).

des, abdominal subcutaneous fat volume and visceral fat volume[27]. A cross-sectional study of 447 children also demonstrated that higher values of blood pressure and lower values of HDL-c were associated with carotid intima media thickness[28]. Together, these results reinforce the role of MetS components with increased risks of atherosclerosis progression in early stages of life.

Therefore, the identification of anthropometric predictors of MetS is crucial in clinical practice, since it can be used as an easy and fast method to suggest and investigate metabolic complication, in order to improve its prognostic and treatment. In the present study, cut off point of waist circumference for MetS diagnosis was found in a sample of 195 obese adolescents (111.5 cm for boys and 104.6 cm for girls), based on the MetS diagnosis proposed by IDF criteria for children and adolescents[24].

In multiple regression analysis adjusted for age and gender, MetS was predicted by waist circumference in a gender-dependent manner. Our analysis indicated that the risks of individuals presenting MetS were raised by 11% for each additional increase of 1 cm in waist circumference (Table III). Moreover, waist circumference was positively correlated with body fat, insulin resistance, insulin, liver enzymes, blood pressure and pro-inflammatory leptin/adiponectin ratio. On the other hand, waist circumference was negatively correlated with insulin sensibility (QUICKI), adiponectin and anti-inflammatory adiponectin/leptin ratio. In agreement, it was demonstrated that waist circumference also correlated with glycemia, HDL-c and blood pressure in a sample of adults[6]. Confirming the importance of waist circumference as an indicator of cardiometabolic risks, we also demonstrated that waist circumference was correlated with the number of MetS parameters.

Visceral fat is closely associated with cardiovascular risk factors. In obese adolescents, visceral fat was the most significant predictor of elevated carotid inti-

ma media thickness, being considered a key predictor of arterial wall thickening. In this way, visceral fat is suggested to be the focus of cardiovascular disease prevention in obese adolescents[27]. The waist circumference is considered an anthropometric method correlated with visceral adiposity in obese adolescents, as we observed in the present study. Although, there are other main methods for examining abdominal fat, such as computed tomography and magnetic resonance, they present high costs and radiation exposure, which limit their application to be used on a large scale in population[29].

Adipose tissue has been considered a secretory organ and a potent source of hormones, peptides and adipokines involved in food intake regulation, glucose and lipid metabolism, inflammation, coagulation and blood pressure control. Furthermore, abdominal obesity has been identified as a particularly harmful fat depot, associated with chronic inflammatory response characterized by abnormal adipokines production and the activation of several pro-inflammatory signaling pathways. This low-grade inflammation is characterized by high levels of TNF-α, IL-6, leptin, c reactive protein, resistin, PAI-1 and low levels of adiponectin. In this way, abdominal obesity is related to the main risk factor to development of pathogenesis of MetS, insulin resistance, NAFLD, cardio metabolic risks and all-cause of mortality[3,5].

One of our objectives was to investigate the prevalence of altered metabolic parameters, such as NAFLD in obese adolescents with and without MetS. MetS obese adolescents presented significantly higher prevalence of NAFLD (69.7% in boys and 58.82% in girls) compared to Non-MetS (32.61% in boys and 22.68% in girls) (Figure 1). The NAFLD can be considered as a hepatic manifestation of MetS. This disease comprises a spectrum ranging from simple steatosis to steatohepatitis, which includes varying degrees of inflammation and fibrosis, progressing to end-stage liver disease with cirrhosis. Recently, it was demonstrated that visceral fat predicts NAFLD, and the risk individuals presenting NAFLD were raised by 60.6% for each additional increase of 1 cm in visceral fat in obese adolescents[12].

Deposition of lipid within the liver represents part of an abnormal lipid partitioning pattern, most commonly associated with high amount of intra-abdominal fat. Lipid deposition in the liver can be a cause of insulin resistance, via local acceleration of lipogenesis, and hepatic insulin resistance, leading to further compensatory hyperinsulinemia and hyperglycemia[30].

We also observed significantly higher values of AST, ALT and GGT in MetS adolescents. Similarly, Fernández-Ruiz et al. (2014)[31] demonstrated that MetS patients presented significant higher values of ALT compared to Non-MetS patients. Corroborating, the literature indicates that elevations in liver enzymes are considered the early surrogate markers of liver dysfunction, such as NAFLD. Moreover, the elevation in liver enzymes is associated with MetS and related to type 2 diabetes, being considered one potential biochemical parameter in clinical practice. Significant increased risk of 1.2-fold of developing type 2 diabetes per 1-SD increment ALT and GGT levels was observed in young adults after a follow up of 16-years[32]. In children and adolescents, Patel et al. (2011)[33] demonstrated that ALT was associated with BMI and some MetS parameters, such as TC, HDL-c and HOMA-IR. The authors concluded that ALT is an established biomarker of ectopic fat accumulation in the liver, and may help improve the risk assessment of MetS and related disorders in the pediatric population, especially adolescents.

A noteworthy fact is the higher prevalence of insulin resistance in MetS obese adolescents compared to Non-MetS group. We observed a significantly higher prevalence of 80% in MetS obese adolescents (78.79% in boys and 82.35% in girls) compared to 46.90% in Non-MetS (54.35 in boys and 43.43 in girls) (Figure 1). Insulin resistance presents a key role in the development of metabolic obesity comorbidities in childhood, being necessary to be considered in clinical practice, since it is suggested as one of the pathophysiological basis of metabolic syndrome[4]. Moreover, insulin resistance was considered an independent predictor of carotid intima media thickness, suggesting its role on atherosclerosis development in obese adolescents[34].

Additionally, MetS obese adolescents presented significantly lower values of adiponectin. Similar result was observed by Calcaterra et al. (2009)[35] who demonstrated that obese children and adolescents also presented significantly lower values of adiponectin, reaching a 10 times greater reduction. This adipokine is secreted in low proportion in obesity condition, and it can present an insulin-sensitizing and an anti-atherogenic role[9]. Adiponectin is believed to reduce atherosclerosis progression by slowing endothelial activation, monocyte and macrophage adhesion and activation, platelet aggregation, and smooth muscle cell proliferation. Adiponectin is also involved in atherosclerosis prevention by increasing nitric oxide, preventing endothelial dysfunction, and by local inhibition of inflammatory molecules. Thus, hypoadiponectinemia directly promotes pathological reactions in cardiovascular system, and can lead to insulin resistance, type 2 diabetes and atherosclerosis formation[36].

In a 16-year longitudinal study conducted with 2196 individuals, low adiponectin levels conferred a higher risk of cardiovascular disease[37]. Corroborating, subjects in the highest tertile of adiponectin had lower risks of having MetS, being adiponectin negatively associated with increased MetS components[38].

On the other hand, in a previous study, leptin predicted MetS in men and women. It was observed that the risk of MetS increased with higher levels of leptin after adjusting for potential confounders in women. Leptin remained independently associated with MetS risk after additional adjustment for adiposity, cytokines and C Reactive Protein[39]. One important data obtained of the

HELENA study conducted in a sample of 927 European adolescents showed that leptin presented significantly progressive and linear increase according to BMI, being positively correlated with BMI during adolescence[40].

Moreover, we are able to show that leptin/adiponectin ratio was significantly higher in girls with MetS compared to Non-MetS (Table II). This ratio has been suggested to be a marker of cardiovascular risks, since it was significantly correlated to MetS parameters, such as, systolic blood pressure, HDL-c and insulin resistance. Moreover, L/A ratio was considered an independent predictor of carotid intima media thickness in adults[41]. Together, these results highlight the importance of controlling metabolic parameters and adipokines in order to prevent and delay future cardiovascular risks associated with obesity.

Park et al. (2013)[42] demonstrated that higher L/A ratios were significantly associated with increased mortality in nondiabetic peritoneal dialysis patients. The impact of the L/A ratio on patient survival remained significant even after adjustments for BMI and other confounding variables. Non-survival patients presented significantly higher values of L/A ratio, which was associated with increased mortality. Although, significant reduction in L/A ratio can be observed with 7% of weight loss in obese adolescents[9].

Our study presents some limitation, such as the sample size of volunteers analyzed. The waist circumference cut-off points proposed in this study need to be explored in a large population of obese adolescents, since the analyzed population is entirely Brazilian. Additional investigation including a control group and long-term follow-up are also needed.

In conclusion, we found that waist circumference is correlated with MetS parameters, inflammatory biomarkers and visceral fat. High prevalence of NAFLD and altered parameters were observed in obese adolescents diagnosed with MetS. Therefore, the results suggest that waist circumference procedure may be a simple and fast method of assessing visceral adiposity, being an indicator of MetS and metabolic alterations to be considered in clinical practice. Finally, we demonstrated the important role of pro/anti-inflammatory adipokines mediating the MetS diagnosis, especially in girls, once we showed high L/A ratio in MetS group and low adiponectin in all analyzed patients.

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