

Metabolic syndrome in overweight/obese female adolescents

Síndrome metabólica em adolescentes do sexo feminino com sobrepeso e obesidade

Síndrome metabólico en adolescentes del sexo femenino con sobrepeso y obesidad

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ABSTRACT

Objective: To evaluate biochemical and physiological variables in overweight/obese and normal body weight female adolescents and assess whether cardiovascular risk factors, postulated as components of the metabolic syndrome, are already present in this age group.

Methods: Cross-sectional study comparing all girls aged between 12 and 18 years from a highschool in Ribeirão Preto, São Paulo, Brazil. Girls were divided in two groups: overweight/obese (n=30) and control (n=39). The following were evaluated: weight, height, skinfolds, circumferences of the abdomen and hip and biochemical parameters (glucose, insulin, lipid profile, urea, creatinine, fibrinogen, PAI-1, ferritin, sodium and microalbuminuria).

Results: Overweight and obese girls had higher levels of blood pressure, glucose, triglycerides, uric acid, PAI-1, fibrinogen and insulin, and lower HDL cholesterol compared with the control group. The analysis of risk factors clusters showed that 76.7% of adolescents from the overweight/obese group had two or more risk factors associated with metabolic syndrome, while 79.5% of the adolescents in the control group had one or none risk factors. Microalbuminuria and serum ferritin did not show differences between groups.

Conclusion: Overweight/obese female adolescents already have hypertension, dyslipidemia, disfibrinolysis, hyperinsulinemia and clusters of cardiovascular risk factors.

Key-words: obesity; hyperinsulinism; insulin; metabolic syndrome X; cardiovascular diseases; adolescent.

RESUMO

Objetivo: Avaliar parâmetros bioquímicos e fisiológicos em adolescentes do sexo feminino com sobrepeso/obesidade ou com peso corporal normal e avaliar se fatores de risco cardiovascular, postulados como componentes da síndrome metabólica, já estão presentes nessa faixa etária.

Métodos: Estudo transversal, tendo-se comparado a totalidade de meninas com idades entre 12 e 18 anos de um colégio de Ribeirão Preto, divididas em dois grupos: sobrepeso/obesidade (n=30) e controle (n=39). De cada menina, foram avaliados parâmetros antropométricos (peso, estatura, dobras cutâneas, circunferências do abdome e do quadril) e bioquímicos (glicose, insulina, lipidograma, ureia, creatinina, fibrinogênio, PAI-1, ferritina, sódio e microalbuminúria).

Resultados: As adolescentes com sobrepeso/obesidade apresentaram níveis maiores de pressão arterial, glicose, triglicérides, ácido úrico, PAI-1, fibrinogênio e insulina e níveis menores de colesterol-HDL em relação ao grupo controle. A análise de alterações e formação de *clusters* de fatores de risco demonstrou que 76,7% das adolescentes do grupo sobrepeso apresentaram dois ou mais fatores de risco relacionados à síndrome metabólica, enquanto 79,5% das adolescentes do grupo controle apresentaram nenhuma ou apenas uma alteração. Os parâmetros microalbuminúria e ferritina sérica não apresentaram alterações e diferenças entre os grupos.

Conclusões: Adolescentes do sexo feminino com sobrepeso/obesidade já apresentam hipertensão, dislipidemias, disfibrinólise, hiperinsulinemia e *clusters* de fatores de risco cardiovascular.

Palavras-chave: obesidade; hiperinsulinismo; insulina; síndrome X metabólica; doenças cardiovasculares; adolescente.

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RESUMEN

Objetivo: Evaluar parámetros bioquímicos y fisiológicos en adolescentes del sexo femenino con sobrepeso/obesidad o peso corporal normal y evaluar si factores de riesgo cardiovascular, postulados como componentes del síndrome metabólico, ya están presentes en esa franja de edad.

Métodos: Estudio transversal, habiéndose comparado la totalidad de niñas con edades entre 12 y 18 años, de un colegio de Ribeirão Preto (Brasil), divididas en dos grupos: sobrepeso/obesidad (n=30) y control (n=39). De cada niña, se evaluaron parámetros antropométricos (peso, estatura, pliegues cutáneos, circunferencias del abdomen y de la cadera) y bioquímicos (glucosa, insulina, lipidograma, urea, creatinina, fibrinógeno, PAI-1, ferritina, sodio y microalbuminuria).

Resultados: Las adolescentes con sobrepeso/obesidad presentaron niveles mayores de presión arterial, glucosa, triglicéridos, ácido úrico, PAI-1, fibrinógeno e insulina y niveles menores de colesterol-HDL respecto al grupo control. El análisis de alteraciones y formación de *clusters* de factores de riesgo demostró que el 76,7% de las adolescentes del grupo sobrepeso presentaron dos o más factores de riesgo relacionados al síndrome metabólico, mientras que el 79,5% de las adolescentes del grupo control presentaron ninguna o solamente una alteración. Los parámetros microalbuminuria y ferritina sérica no presentaron alteraciones y diferencias entre los grupos.

Conclusiones: Adolescentes del sexo femenino con sobrepeso/obesidad ya presentan hipertensión, dislipidemias, disfibrinólisis, hiperinsulinemia y *clusters* de factores de riesgo cardiovascular.

Palabras clave: obesidad; hiperinsulinismo; insulina; síndrome X metabólico; enfermedades cardiovasculares; adolescente.

Introduction

Overweight and obesity are clinical conditions that are becoming ever more common in Brazil and which constitute risk factors for certain diseases, such as diabetes mellitus (DM) and cardiovascular diseases (CVD)⁽¹⁾. Cardiovascular diseases are a major public health concern because of the high levels of morbidity and mortality with which they are associated. The World Health Organization (WHO) estimates that around 50 to 75% of the world's population is overweight⁽²⁾ and population studies conducted in Brazil demonstrate that the country is also following this trend⁽³⁾. Obesity in childhood

and adolescence is directly linked with obesity in adulthood⁽⁴⁾. Obese adolescents are very likely to become obese adults⁽⁵⁾ and the risk factors for CVD can already be detected at this age⁽⁶⁾. Over the years many different population studies have shown that cardiovascular risk factors (central obesity, reduced glucose tolerance, dyslipidemia and hypertension) are more likely to occur in combination (in clusters) than individually and are often associated with elevated insulin levels⁽⁷⁾. This presentation has been given a variety of different names, but the WHO currently recommends using the term metabolic syndrome⁽⁸⁾. In addition to assessing glycemic profiles, waist circumference, arterial blood pressure and lipids, which assess the classic components of the metabolic syndrome, some studies have also investigated hyperuricemia⁽⁹⁾, increases in serum ferritin⁽¹⁰⁾ and abnormalities of the inflammatory and fibrinolytic systems⁽¹¹⁾ as possible additional components.

The objective of this study was to investigate whether female adolescents with overweight and obesity already exhibit the physiological and biochemical disorders associated with metabolic syndrome.

Method

This study was conducted at the Center for Child and Adolescent Health and Nutrition Research at the Universidade de Ribeirão Preto (Unaerp), in the state of São Paulo, Brazil, between May 21st and September 20th of 2001.

This was a cross-sectional study of the 69 out of 92 female students at the Colégio Tecnológico da Unaerp who met the inclusion criteria. The reason that only girls were studied is that it is possible to clearly define the time they reach puberty using menarche as a marker. The inclusion criteria were female sex, post-menarche and age from 12 to 18. The exclusion criteria were acute diseases during the previous 2 weeks (n=8); known hematological diseases, except iron deficiency anemia (n=0); medication that could interfere with the laboratory analyses (n=2); absence of guardian's signed consent for blood samples and participation in the study (n=13) and problems preventing anthropometric measurements from being taken correctly (n=0).

After application of the above criteria, 69 adolescent girls were enrolled on the study and divided into two groups: overweight/obesity (n=30) and control (n=39). The two groups were formed on the basis of body mass index (BMI) percentiles. Body composition was assessed using the sum of subscapular and tricipital skin folds, measured with a Harpenden adipometer, and the Guedes protocol⁽¹²⁾ was used to estimate percentage body fat.

Adolescents with BMI percentile >85 and body fat percentage $\geq 25\%$ were classified as belonging to the overweight/obesity group. The waist to hips ratio (WHR) was used to define the presence of central adiposity. The WHR is calculated by dividing the waist circumference (cm) – measured at the midpoint between the last rib and the iliac crest, at the midclavicular plane – by the hip circumference (cm) – measured at the iliac crest. A WHR greater than or equal to 0.85 was considered suggestive of central adiposity. Blood pressure was measured and assessed according to the III Brazilian Consensus on Arterial Hypertension⁽¹³⁾.

Blood samples were taken after 12 hours' fasting and patients were instructed to collect urine for 24h. Blood glucose, cholesterol, triglycerides, HDL cholesterol, urea and creatinine tests were conducted using enzymatic kits (Labtest) in an automated Cobas Mira Plus Roche system. Fibrinogen analyses were conducted with the coagulometric method using a DadeBehring kit in a semiautomatic Fibrintimer II Behring system; plasminogen activator inhibitor-1 (PAI-1) assays were conducted with DadeBehring colorimetric kits; serum ferritin was analyzed using an immunoenzymatic fluorescent method in an automatic Mini Vidas BioMérieux system; serum and urine sodium assays were conducted using the ion-selective electrode method in an automatic AVL 9140 system; microalbuminuria was determined using nephelometry in an automatic Nefelômetro BN 100 system; insulin was assayed by chemiluminescence in an automatic Access BioRad system and insulin resistance (IR) was assessed by HOMA testing, using the following mathematical formula: $\text{glucose (mmol/L)} \times \text{insulin } (\mu\text{UI/mL}) / 22.5^{(14)}$.

Statistical analyses were conducted using Student's *t* test and a significance level of $p < 0.05$. For the purposes of this study, the term "cluster" is used to define the co-occurrence of two or more different metabolic syndrome indicators. This aspect is presented descriptively, with no statistical comparisons.

All participants provided signed free and informed consent forms and the project was approved by the Research Ethics Committee at Unaerp.

Results

Table 1 lists the anthropometric characteristics of the adolescents in the two study groups. It will be observed that WHR was greater than 0.85 in 50% of the adolescents in the overweight/obesity group.

Table 2 shows the mean results for cardiovascular risk factors in the two groups. The parameters glucose, insulin, HDL cholesterol, triglycerides, PAI-1, fibrinogen, uric acid, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were all significantly different between groups, with figures higher in the overweight group for all parameters except HDL cholesterol, which was lower in the overweight group. The factors cholesterol, LDL cholesterol, microalbuminuria, creatinine, urea, serum and urine sodium and serum ferritin were not significantly different between groups.

With relation to insulin levels, 43.3% of the adolescents in the overweight group had hyperinsulinemia. The results for peripheral insulin resistance from the HOMA test were 4.0 ± 4.48 and 1.38 ± 0.84 for the overweight and control groups respectively.

Forty percent of the adolescents in the overweight group had hypertension, compared with zero in the control group. Adolescents in the overweight group had significantly higher SBP and DBP results than those in the control group ($p < 0.01$).

Analysis of the percentage distribution of risk factor clusters demonstrated that 76.7% of the adolescents in the overweight group had two or more risk factors in conjunction and 79.5% of the adolescents in the control group had one or zero risk factors. On the basis of the WHO definition of metabolic syndrome, which includes dyslipidemia, systemic arterial hypertension (SAH), central adiposity, microalbuminuria and insulin resistance, together with the proposal to include dysfibrinolysis and hyperuricemia, 43.3% of the adolescents in the overweight group had results suggestive of metabolic syndrome.

Table 1 - Anthropometric characteristics of female adolescents in overweight and control groups, shown as mean \pm standard deviation

	Group I (Control) n=39	Group II (Overweight/obesity) n=30
Age (years)	15.7 \pm 1.8	14.3 \pm 1.8
Weight (kg)*	56.0 \pm 6.0	81.0 \pm 9.0
Height (cm)	160.0 \pm 7.0	160.0 \pm 10.0
Body fat (%)*	23.9 \pm 4.3	38.8 \pm 0.8
WHR	0.77 \pm 0.04	0.85 \pm 0.07*

WHR: waist to hips ratio. * $p < 0.01$ with relation to the control group

Table 2 - Cardiovascular risk factors in female adolescents overweight and control groups, shown as mean \pm standard deviation

	Group II (Control) n=39	Group II (Overweight/obesity) (n=30)
Glucose (mg/dL)*	81.1 \pm 1.2	88.3 \pm 9.4
Insulin (μ U/mL)**	6.7 \pm 3.7	17.1 \pm 13.5
Cholesterol (mg/dL)	156.1 \pm 12.5	162.1 \pm 12.7
HDL Cholesterol (mg/dL)**	47.6 \pm 11.9	39.2 \pm 8.7
LDL Cholesterol (mg/dL)	93.1 \pm 29.5	102.3 \pm 21.6
Triglycerides (mg/dL)**	75.2 \pm 8.7	110.1 \pm 10.5
PAI-1 (U/mL)**	1.2 \pm 1.1	5.9 \pm 2.8
Fibrinogen (mg/dL)**	296.3 \pm 55.1	349.8 \pm 66.8
Microalbuminuria (mg/24h)	15.5 \pm 26.5	9.7 \pm 10.4
Uric acid (mg/dL)**	4.6 \pm 1.2	5.8 \pm 1.1
Creatinine (mg/dL)	0.8 \pm 0.1	0.8 \pm 0.1
Urea (mg/dL)	24.8 \pm 8.2	23.3 \pm 7.1
Sodium (mEq/L)	140.7 \pm 3.3	139.4 \pm 1.7
Ferritin (μ g/dL)	34.1 \pm 24.8	48.7 \pm 37.6
Urinary sodium (mEq/24h)	89.4 \pm 76.1	116.3 \pm 96.4
SBP (mmHg)**	99.6 \pm 9.9	120.8 \pm 16.7
DBP (mmHg)**	66.2 \pm 8.1	78.5 \pm 13.7

PAI-1: plasminogen activator inhibitor-1; SBP: systolic blood pressure; DBP: diastolic blood pressure. * $p < 0.05$. ** $p < 0.01$

Discussion

The results of this study should be treated with caution, given the small number of participants and the fact that only girls were recruited, which limits the potential for generalization. On the other hand, the relevance of these data lies in the fact that there are relatively few studies in the scientific literature that have simultaneously analyzed blood tests, clinical examination results and body composition and also included healthy-weight adolescents for the purposes of comparison. Furthermore, faced with the absence, to date, of an international consensus on the definition of metabolic syndrome in adolescence, this study makes a contribution to the debate with an analysis of a very wide range of biochemical parameters including the classic variables such as lipid profile, glycemia and insulin, and others that are not generally investigated, such as PAI-1, fibrinogen and microalbuminuria, among others. Therefore, both the cardiovascular risk factors that have already been accepted as applying to all age groups and also others that have so far only been studied in adults, were described and compared across the two groups with the intention of assessing the possibility that overweight and obese girls are at greater risk.

The higher glucose, triglycerides and uric acid levels and lower HDL cholesterol level observed in the overweight

group in comparison with the control group are in line with results published by Lind, Berne and Lithell⁽¹⁵⁾ who observed that these findings were more common among people with insulin resistance. The results related to the lipid profile are in line with a study conducted in Taiwan where it was shown that overweight female adolescents had significantly higher triglycerides and lower HDL cholesterol levels⁽¹⁶⁾.

It is important to investigate cardiovascular risk variables early in life in order to prevent atherosclerosis⁽¹⁾. Obese children tend to have high pressure, high triglycerides and lower HDL cholesterol, in common with what is observed in adolescents and young adults⁽¹⁷⁾. Systemic arterial hypertension is part of the metabolic syndrome and it has been repeatedly shown that SAH is independently associated with DM and dyslipidemia, even in people who are not overweight⁽¹⁸⁾. In such cases the increased insulin levels can lead to increased activity in the renin-angiotensin-aldosterone system and reduced sodium excretion⁽⁵⁾. In this study no abnormalities were detected in the serum or urine sodium levels of the adolescents studied and there were no significant differences between the groups. Hyperinsulinemia may also contribute to raising blood pressure by stimulating the sympathetic nervous system⁽¹⁹⁾. Obesity further aggravates insulin resistance and hyperinsulinemia, since it has already been demonstrated that hypertensive obese people have even higher insulin levels in response to

glucose overload, when compared with hypertense people who are not obese⁽²⁰⁾.

Insulin's capacity to stimulate glucose uptake varies from person to person. The pancreatic beta cells attempt to produce sufficient insulin to maintain glucose at normal levels. If this is not possible then type 2 DM can develop, which is a condition that is being observed with ever increasing frequency among the young and which is concurrent with increasing obesity, particularly among adolescent women⁽²¹⁾. Insulin resistance is an abnormality that is detected in patients with type 2 DM; it is present many years before the disease manifests, it has a large hereditary component⁽²²⁾ and it is highly prevalent among obese children⁽²³⁾. The presence of clusters of cardiovascular risk factors observed in this study's overweight group together with their insulin resistance (IR) results (obtained using the HOMA test) indicate that it is necessary to initiate preventative measures to reduce the risk of type 2 DM and CVD among adolescents. With regard to the HOMA test, it is important to point out the possibility of assessment errors in the pediatric age group, since the age-related variation reported in other studies was not taken into account here⁽²⁴⁾.

It has recently been suggested that both reduced fibrinolysis caused by increased PAI-1 and fibrinogen levels⁽¹¹⁾ and also hyperuricemia⁽⁹⁾ should be added to the list of metabolic syndrome components, since they increase the risk of the atherothrombotic complications observed in obesity and type 2 DM⁽¹¹⁾. In this study, it was observed that these factors were outside the normal range in the overweight group, which is further evidence of the need for prevention in this age group.

The mechanisms that explain the association between high PAI-1 levels and obesity have not yet been fully elucidated, but the possibility of a link with insulin resistance via increased endothelial production⁽²⁵⁾ or via PAI-I production by adipose tissue has been considered⁽²⁶⁾.

The results show that there was no significant difference between microalbuminuria levels between the adolescents in the two study groups. These results may be the result of the fact that microalbuminuria is more closely linked with complications of type 2 DM and SAH – which have not yet emerged in the age group studied here – than with insulin resistance and dyslipidemia⁽²⁷⁾.

Serum ferritin has been proposed as a cardiovascular risk factor, since some studies have found positive correlations between serum ferritin concentrations and glucose and triglycerides, and an inverse correlation with HDL cholesterol⁽¹⁰⁾. Elevated iron reserves may increase lipid peroxidation, especially of free fatty acids, via free radical production, since ferrous iron is a potent catalyst for this reaction⁽²⁸⁾. This alteration was not detected, however, and so for the sample studied here ferritin was not part of the constellation of metabolic abnormalities linked to overweight. This fact may be partly caused by the elevated iron deficiency prevalence among Brazilian adolescents, contributing to low baseline ferritin levels⁽²⁹⁾.

In conclusion, the overweight adolescents analyzed here already exhibit a tendency to SAH, dyslipidemia, dysfibrinolysis, hyperinsulinemia and increased uric acid and central adiposity, indicating a need to act to prevent the metabolic syndrome while those at risk are still adolescents.

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