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Original/*Pediatría*

Metabolic syndrome and its components are strongly associated with an inflammatory state and insulin resistance in the pediatric population

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Abstract

Introduction: **Endothelial inflammation and insulin resistance (IR) begin in childhood and constitute the pathophysiological basis of Metabolic Syndrome (MS). The increase levels in plasma of inflammatory markers such as high sensitive PCR (hsPCR), plasminogen activator inhibitor 1 (PAI-1) and tests suggestive of IR such as Insulin (Ins) and alanine aminotransferase (ALT) have been associated with MS in adults, but have not been studied in children.**

Objectives: **Correlate the presence of MS and its components with the inflammatory and IR markers seen in the pediatric population.**

Methods: **Cross-sectional study of 337 children (10,9±9,7 years) whose levels of hsPCR, PAI-1, Ins and ALT were determined, along with their association with MS and its individual components.**

Results: **37 children had MS (10,4%). The frequency of MS components was: abdominal obesity 38,5%, hypertension (HTN) 21,3%, hypertriglyceridemia 17,8%, HDL 21,3% and hyperglycemia 1,4%. hsPCR, PAI-1, ALT and Ins were higher in the presence of MS and increased progressively when components were came together.**

Conclusions: **The pediatric population segment with MS had a higher concentration of hsPCR, PAI-1, Ins and ALT.These levels increase proportionally MS components add up, suggesting that even before diagnosis criteria are fulfilled there is a inflammatory state.**

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Key words: *Metabolic syndrome*. *Inflammatory markers*. *Obesity*. *Pediatric*.

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SINDROME METABÓLICO Y SUS COMPONENTES SE ASOCIAN CON INSULINO RESISTENCIA Y MARCADORES DE INFLAMACIÓN EN POBLACION PEDIÁTRICA

Resumen

Introducción: **La insulino resistencia (IR) y la inflamación endotelial constituyen la base fisiopatológica del Síndrome metabólico (SM) . El aumento de los niveles plasmáticos de mascadores de inflamación como PCRus, Inhibidor del activador de plasminógeni tipo 1 (PAI-1) y parámetros sugerentes de insulino resistencia (IR) como insulina, triglicéridos y Alanino aminotransferasa (ALT) se han asociado a síndrome metabólico en adultos pero han sido menos estudiados en pediatría. .**

Objetivo: **Correlacionar los componentes del SM con marcadores de inflamación e IR en población pediátrica.**

Métodos: **Estudio transversal de 337 niños (10,9±9,7 años). Se determinó niveles plasmáticos de PCRus, PAI-1, ALT e Insulina y se evaluó su asociación con Síndrome metabólico y sus criterios de forma individual.**

Resultados: **37 sujetos tuvieron diagnóstico de SM (10.4%). 38.5% presentó obesidad abdominal, 21.3% Hipertensión arterial, 17.8% Hipertrigliceridemia, 21.3% niveles bajos de HDL y un 1.4% Hiperglicemia. Encontramos que PCRus, PAI-1 y ALT fueron más altas en presencia de SM y aumentaban progresivamente a medida que se agregaban criterios diagnósticos.**

Conclusión: **Este estudio demuestra que en población pediátrica con diagnóstico de SM existen niveles más altos de PCRus, PAI-1, ALT e insulina y que a mayor número de criterios presentes la inflamación pareciera ser mayor lo que sugiere que incluso antes de tener el diagnóstico de SM ya existe un estado pro inflamatorio.**

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Palabras clave: *Síndrome metabólico*. *Marcadores inflamatorios*. *Obesidad*. *Pediatría*.

Introduction

Metabolic syndrome (MS) was described by Reaven[1] in 1988 to bring together a series of cardiometabolic abnormalities linked to increase atherogenic risk and cardiovascular disease in adults. Atherosclerosis is a progressive process that starts in childhood and is modulated by a series of inflammatory mediators related to the beginning of atheroma and the appearance, at a later age, of plaque disruption, which in the case of coronary arteries results in myocardial disease[2-3]. The atherosclerotic process can be accelerated by the presence of risk factors such us obesity, sedentarism, hypertension, dyslipidemia and family history of premature cardiovascular disease[4]. Some of these have been grouped as the Metabolic Syndrome (MS), which would be capable of predicting early atherosclerosis, increased risk of cardiovascular disease and type 2 Diabetes Mellitus (DM2) better than its individual components. It has also been associated with biochemical, functional or anatomical injuries of the endothelium, which together are known as endothelial damage. The coexistence of 3 or more of its components represents a synergistic effect on these risks wich has been confirmed by anatomopathological studies with atheroma and fatty streaks in coronary arteries and the aorta in people as young as 10 years old. Moreover, more refined subclinical endothelial inflammation markers have been developed, such as hsCRP, PAI-1, tumor necrosis factor α (TNF-α) and adiponectin[2,5,6,10]. hsPCR has been one of the most studied and validated markers of endothelial damage in adult patients with coronary heart disease, showing that its elevated levels in patients with intermediate risk independently predict a greater risk of cardiovascular events[7,12-14].

Worldwide, and especially in our country, there is a progressive increase in childhood obesity, reaching approximately 20% among first year primary Chilean school students[14]. The inflammation state that accompanies obesity is considered to be a chronic low-grade inflammation, generally associated with high concentrations of leukocytes, fibrinogen and other inflammatory biomarkers, such as hsPCR. There is strong evidence that links increased body fat, especially abdominal and hepatic fat, to cardiovascular risk factors[10,14]. A recent study by our group identifies a 10,4% prevalence of MS in healthy school children, which increases in proportion to body mass index (BMI), up to 35,1% in obese[15]. Moreover, studies of north American children and adolescents show a 31% incidence of MS in patients with BMI >p85, which shows the dimension that this problem is reaching[5,16].

Because the atherosclerotic process and endothelial damage starts in the first decade of life and progresses into adulthood, early identification of children with greater cardiometabolic risk is vital, in order to reduce the progression of the disease through changes in lifestyle performed with a multidisciplinary approach. Most MS components are potentially reversible with lifestyle changes[17] in children and adolescents, as in adults.

Although multiple clinical studies in the last 20 years have attempted to define MS in adults, determined its association with subclinical inflammation and IR and preventive treatments, its usefulness in clinical practice is still controversial. Although MS diagnosis is increasing progressively, there are no studies in children with strong scientific evidence to support its clinical utility, and there is no universally accepted definition[19].

Therefore, new subclinical inflammation markers have been studied, in both adults and children, which predict this risk independently from MS, such as hsPCR and PAI-1[18-20], in addition to markers whose elevation has been associated with IR, such as Ins[22], ALT[23] and MA[24].

The aim of this study is correlate the presence of MS and its distinct components, with endothelial inflammation and IR markers in a pediatric population.

Subjects and methods

Subjects: A cross-sectional design was used for this study. The subjects were evaluated at the pediatric endocrinology and nephrology clinics of the Pontificia Universidad Catolica de Chile from July 2009 to March 2010. A total of 337 Chilean children and adolescents children were enrolled.

Methods: All patients underwent a complete physical examination performed by two paediatric endocrinologists (AM & HG) and one paediatric nephrologist (MA). Height was measured using a wall-mounted Harpenden stadiometer (Holtain, UK). Weight and total body fat mass percentage were assessed by bioelectrical impedance (Tanita, Corporation of America, Arlington Heights IL, USA). The body mass index (BMI) was calculated. Overweight was defined as BMI ≥p85 and obesity ≥p95. Waist circumference (WC) was obtained with an inextensible tape on the edge of the iliac crests, averaging 3 measurements. Abdominal obesity was diagnosed with WC >p90 of the NHANES survey[29].

Trained nurses measured the BP and heart rate of all subjects. While the patient was in a seated position, three consecutive measurements were taken on the right arm every 5 min using the oscillometric method (Dinamap CARESCAPE V100, GE Healthcare; Medical Systems Information Technologies, Inc., Milwaukee, WI, USA). This technique was performed following the published recommendations with a cuff and bladder size adjusted to the upper arm girth. All subjects with elevated BP were confirmed to be hypertensive using the auscultatory method. The BP of children was classified according to the Seventh Report of Task Force[26].

With the aim of comparing blood pressure in children of different genders, ages and statures, we calculated the BP index. The BP index was determined by

using the observed BP/50th percentile BP for gender, age and stature using the standard reported values.

MS was defined using the modified Cook Criteria: WC >p90, HDL cholesterol (HDL) ≤40mg/dL, triglycerides (TG) >110mg/dL, glycemia >100mg/dL and systolic or diastolic blood pressure ≥p90[27].

Biochemical study

Following an overnight fast, basal blood samples were obtained between 8:00 and 10:00 AM to measure: Glycemia, insulin, Lipid profile: Total cholesterol (TC), HDL cholesterol (HDL), LDL cholesterol (LDL), and Triglycerides (TG). ALT, hsPCR, PAI-1 and Microalbuminuria (MA).

Laboratory assay

Glycemia was determined using the glucose-oxidase method, TC, HDL, LDL and TG using the colorimetric method. ALT was determined using the Roche enzymatic UV test with a sensitivity of 4U/L. hsPCR were analyzed by nephelometry with an Image auto-analyzer with a sensitivity of 0.2mg/L. Ins were analyzed by an ADVIA Centaur direct chemical luminometric immunoassay with a sensitivity of 5μUI/mL. PAI-1: Blood samples were collected avoiding any blood activation on 0.109 M citrate anticoagulant. Plasma PAI-1 was measured by ELISA according the manufacturer's instructions (Zymutest PAI-1 antigen, HYPHEN BioMed, France). The inter assay variation were 9.4% and 8.1% for high and low controls, respectively. MA was analyzed by nephelometry with an Image auto-analyzer with a sensitivity of 0.2mg/dL. MA was expressed per milligram of creatinine in urine.

Statistical Analysis

Categorical variables were described in terms of frequency and percentage, and the numerical variables in terms of median and range. Distribution of numerical variables was evaluated by the Shapiro–Wilk test. Association between categorical variables and numerical variables was evaluated by the Mann-Whitney test and the correlation among numerical variables by the Spearman correlation coefficient calculation. A p-value less than 0.05 was considered significant. The analyses were conducted using SPSS software version 15.0. The results of variables not normally distributed were expressed as medians.

Results

The average age was 10.9±9.7 years (range: 4.9-15.6) and 52.5% were male. The BMI z-score was +1.0 ± 2.1SD, 33.2% were obese and 25,5% overweight. We found 10,9% (n=37) of the children with the full diagnostic criteria for MS. No significant differences were found to age, sex, family history of hypertension or Diabetes Mellitus among children with and without MS.

The frequency of the different MS components were: abdominal obesity 38,5% (130/337), hypertension 21,3% (72/337), hypertriglyceridemia 17,8% (60/337), high HDL cholesterol 21,3% (71/337) and hyperglycemia 1.4% (4/337) (Fig. 1). Of the 37 children with MS,

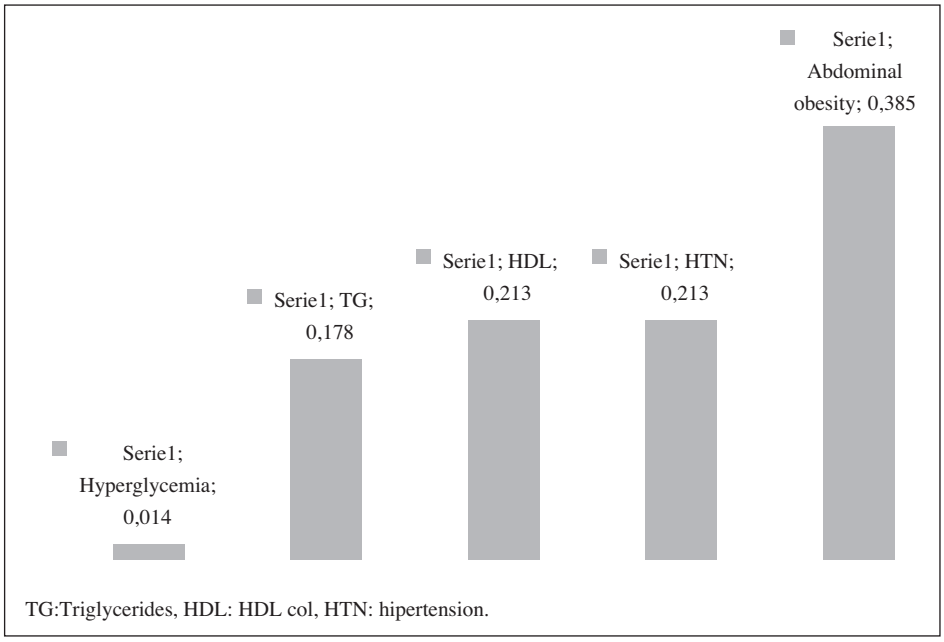

Fig. 1.—Frequency of the different MS componentes in the total sample.

86,4% were obese and 13,5% overweight. Abdominal obesity and hypertension were present in 100% and 65% of the children with MS, respectively.

In the presence of MS (n=37) the following parameters were higher than the group without MS (n=300): hsPCR=2.2 (0.2-19) mg/L vs 0.6 (0.2-25.6) mg/L (p<0.01); ALT=20 (7-95) U/L vs 15 (6-89) U/L (p<0.01); insulin 9.5(4.8-67.3) μIU/ml vs 7.3 (4.5-29.4) μIU/ml (p<0.01) and PAI-1=33 (6.3-75.4) ng/ml vs 18.1 (1.1-56.2) ng/ml (p<0.01) (Fig. 2). They increase progressively with an increasing number of MS components present, which is statistically significant (p<0,01) (Fig. 3). We did not include an analysis of subjects with 5 MS components, because there was only 1 case in our series. In our study there was no correlation between MS and microalbuminuria. Neither was there an increase in its value as MS components were added up (Table I).

Discussion

Our study shows that hsPCR, PAI-1, ALT and insulin are related to the presence of MS in the pediatric population, and they increase as its components are added up, which suggests that a pro-inflammatory state and/or IR exists in different parenchyma even before meeting the fulfilled MS diagnostic criteria (3 or more components). It also indirectly validates these markers for possible future clinical use.

Further studies are needed to determine which levels of these markers are associated with increased cardiometabolic risk and attempt to determine a cutoff point that better defines this risk in children.

The increase in ALT observed in the children in the evaluated sample could be corresponds to nonalcoholic fatty liver disease (NAFL), so further studies should be conducted to correlate biochemical markers with images or even liver biopsy to confirm this diagnosis. NAFL has been described as a prelude of type 2 Diabetes in Hispanic adolescents (ref nuestra)

Only four patient in our series had impaired fasting glycemia, which is consistent with other publications[14], and which questions the usefulness of this MS diagnostic criterion in this age group. It simultaneously opens the possibility of using some of these markers as a new diagnostic criterion once normal pediatric population levels are defined.

It is known that abdominal obesity plays a fundamental role in MS development. This has been confirmed in our study in which 100% of children with MS had abdominal obesity.

Our study suggests that the aggregation of individual components of the SM predicts cardiometabolic risk better than diagnosis of MS itself.

Our study does not examine the individual weights of each MS components, but demonstrates that this risk increases progressively from sense the presence of one of them. Our results suggest that with 2 or more MS components is fully justified to perform a timely and multidisciplinary treatment aimed to reversing inflammatory states and IR, which in the future could produce type 2 Diabetes Mellitus and coronary heart disease. Further studies are important to weigh the MS components individually, because each component carries a certain individual risk which depends on envi-

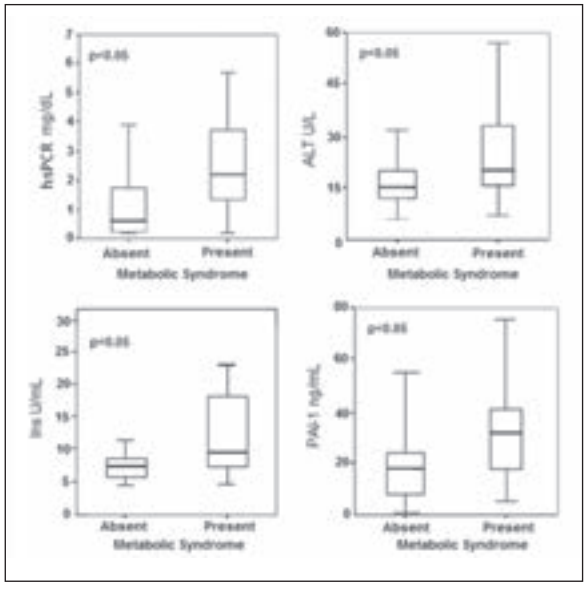

Fig. 2.—Median of the markers according to the presence or absence of SM.

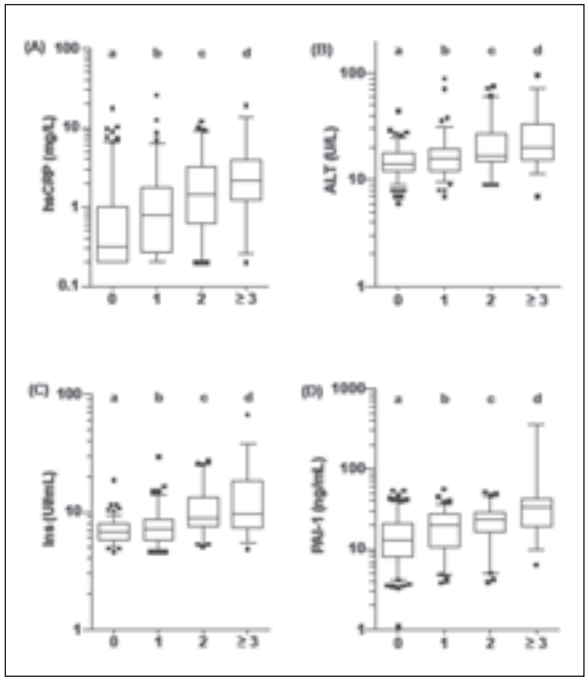

Fig. 3.—Relationship between MS componentes and studied markers.

Table I
Relationship between the number of MS components and each marker

MS components	*0 (n=147)*	*1 (n=93)*	*2 (n=60)*	*3 (n=23)*	*4 (n=13)*	*p*
hsPCR mg/dL	0,3 (0,2-17,7)	0,8 (0,2-25,6)	1,4 (0,2-12,1)	1,8 (0,2-12,7)	3,6 (0,4-19,0)	<0,01
PAI-1 ng/mL	13,0 (1,1-54,0)	20,3 (3,7-56,2)	23,5 (3,9-51,4)	30,6 (10,2-50,7)	35,9 (6,3-75,4)	<0,05
Ins UI/mL	6,8 (4,6-18,6)	7,1 (4,5-29,4)	8,9 (5,1-27,1)	9,1 (4,8-20,1)	16,1 (6,7-67,3)	<0.05
ALT U/L	14,0 6,0-44,0	16,0 7,0-89,0	17,0 9,0-75,0	19,0 12,0-69,0	21,0 7,0-95,0	<0.05
MA μg/mg	3,6 (1,0-324)	3,6 (1,0-104)	3,2 (1,0-196)	2,8 (1,0-10,3)	7,9 (1,0-81,1)	ns

PAI 1: plasminogen activator inhibitor 1; Ins: insulin; ALT: alanine aminotransferase; MA: microalbuminuria.
Values shown as medians and ranges.

ronmental and genetic factors and some of them may be more important than others.

Earlier studies by another group of our institution showed that the sum of 2 or more MS components is associated with increased intima-media thickness of the carotid artery[28,29]. These results are similar to those found in our study, although there is no consensus in the application of these findings.

Our study provides evidence that children with several components of MS mainly have a inflammatory state and/or IR, appearing even before meeting the fulfilled diagnostic criteria, with an adequate number of studied subjects, conducted prospectively and simultaneously measuring physical and biochemical parameters. Our population segment has a high percentage of obesity. This does not invalidate our results, because our study does not attempt to know MS prevalence, but rather of the correlation of its components with new markers of early endothelial damage.

Studies with a representative sample of the general population may be able to reduce bias and determine the normal levels of these markers in pediatric age, since they could be a useful tool for determining the presence of endothelial inflammation in children and in the future could be helpful to properly estimate cardiometabolic risk in our children.

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No potential conflicts of interest relevant to this article were reported.

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