



## Assessment of endothelial function and intima-media thickness in Mexican children with metabolic syndrome: a cross sectional study

*Evaluación de la función endotelial y del grosor de la íntima-media en niños mexicanos con síndrome metabólico: un estudio transversal*

Nilda Espinola-Zavaleta,\* Luis Eduardo Enríquez-Rodríguez,\* Irma Miranda-Chávez,\*\* Jessy Steve Masso-Bueso,\* Isabel Carvajal-Juárez,\* Erick Alexanderson-Rosas,\* Aloha Meave-González\*\*\*

\* Departamento Medicina Nuclear.  
\*\* Consulta Externa de Pediatría.  
\*\*\* Departamento de Resonancia Magnética Nuclear.

Instituto Nacional de Cardiología «Ignacio Chávez».

Corresponding author:  
**Nilda Espinola Zavaleta, M.D., PhD**  
Departamento de Medicina Nuclear.  
Instituto Nacional de Cardiología «Ignacio Chávez».  
Juan Badiano Núm. 1,  
Col. Sección XVI,  
Tlalpan, 14080,  
Ciudad de México,  
México.  
Teléfono: 55732911,  
ext. 1196 o 1426  
Fax: 5606 3931  
E-mail:  
niesza2001@hotmail.com

**ABSTRACT. Introduction:** Metabolic syndrome (MS) is a well-known risk factor for the development of cardiovascular disease. **Objective:** The aim of this study was to compare the endothelial function and intima-media thickness, in children with MS vs control group to determine the existence of mechanisms of atherosclerosis. **Material and methods:** Cross sectional study that included children with MS and controls (15 patients in each group) were studied. Systolic pulmonary artery pressure (SPAP), flow-mediated vasodilation (FMV) and intima-media thickness (IMT) were assessed. **Results:** The FMV in MS was diminished compared with control ( $8.7\% \pm 1.6$  vs  $12.9\% \pm 1.2$ ;  $p < 0.0001$ ). FMV was less than 10% in 73% of MS group vs 13% of controls. IMT was increased in MS ( $0.06 \pm 0.002$  vs  $0.034 \pm 0.005$ ;  $p < 0.001$ ). In the MS group, SPAP was increased ( $37.8 \pm 14.4$  vs  $23.2 \pm 5.31$ ;  $p < 0.002$ ). A negative correlation between FMV and IMT was found ( $r = -0.562$ ). **Conclusion:** In our study, metabolic syndrome group had an increased of IMT and SPAP and a decreased FMV. These findings should relate with the initial mechanism of the atherosclerosis from the infancy. **Key words:** Metabolic syndrome, flow-mediated vasodilation, intima-media thickness.

**RESUMEN. Introducción:** El síndrome metabólico (SM) es un factor de riesgo para el desarrollo de enfermedad cardiovascular. **Objetivo:** Comparar la función endotelial y el grosor íntima-media en niños con SM y niños sanos, para determinar la existencia de mecanismos de aterosclerosis temprana. **Material y métodos:** Estudio transversal que incluyó dos grupos: 15 niños con SM y 15 sanos. Se determinó: presión sistólica de la arteria pulmonar (PSAP), vasodilatación mediada por flujo (VMF) y grosor íntima-media (GIMc). **Resultados:** La VMF en niños con SM fue inferior a la de los sanos ( $8.7 \pm 1.6\%$  vs  $12.9 \pm 1.2\%$ ,  $p < 0.0001$ ). En el 73% de niños con SM y en el 13% de sanos la VMF fue menor al 10%. El GIMc fue mayor en SM ( $0.06 \pm 0.002$  vs  $0.034 \pm 0.005$ ,  $p < 0.001$ ). En SM la PSAP fue mayor ( $37.8 \pm 14.4$  vs  $23.2 \pm 5.31$ ,  $p < 0.002$ ). Existió correlación negativa entre la VMF y el GIMc ( $r: -0.562$ ). **Conclusiones:** Los niños con SM tuvieron una VMF disminuida, incremento en el GIMc y PSAP, lo cual podría relacionarse con aterosclerosis temprana.

**Palabras clave:** Síndrome metabólico, vasodilatación mediada por flujo, grosor íntima-media.

### INTRODUCTION

Metabolic syndrome (MS) is a global epidemic that also affects children. Prevalence according to panel III (ATP III) modified version of MS for children and teenagers (which includes

abdominal obesity, atherogenic dyslipidemia, high blood pressure, glucose intolerance, proinflammatory and prothrombotic state), is approximately 4.2% and continues to rise.<sup>1</sup>

Endothelial dysfunction is one of the initial features of MS and characterizes by



diminished vasodilatation and/or paradoxical vasoconstriction of distal or coronary arteries in response to a nitric oxide (NO) liberating stimuli. Such response is observed in the early stages of the atherosclerotic process and may be quantified through the measurement of brachial artery flow mediated dilatation.

Endothelial dysfunction has been documented in children with at least one of the MS components: insulin resistance,<sup>2,3</sup> central obesity,<sup>4-10</sup> arterial hypertension,<sup>10</sup> atherogenic dyslipidemia<sup>11,12</sup> or a combination of the anterior;<sup>5</sup> but few studies have evaluated endothelial function directly in this group of patients. Therefore, the aim of this study is to assess endothelial function and intima-media thickness in children with MS compared with a control group.

## MATERIAL AND METHODS

Cross sectional study include children between the ages 3 to 17 years old were enrolled, in a period from November 2005 to July 2007, in the *Instituto Nacional de Cardiología «Ignacio Chávez»*. Two groups were compared: 15 participants in the MS group (body mass index  $\geq 25\text{kg/m}^2$ ) vs. 15 in the control group, paired by age and sex. ATP III criteria was used to define MS. Children were evaluated by two expert pediatric cardiologists and an echocardiographic comprehensive evaluation was carried out. Exclusion criteria were children with congenital or acquired heart disease.

Echocardiographic evaluation was performed with a Phillips Sonos 5500 ultrasound system, with an S3 transducer. Left ventricular systolic function was determined

with the biplane method of disks. Systolic pulmonary artery pressure (SPAP) was estimated with Bernoulli equation using maximal velocity of tricuspid regurgitation jet acquired with continuous Doppler in the apical four chamber view.

Endothelial function evaluation was performed with a Phillips Sonos 5500 high resolution vascular ultrasound and a linear transducer of 3 to 11MHz. Brachial artery dilatation was measured according to previously established rules.<sup>13</sup> Left arm extension and immobilization is required to allow access to the brachial artery. Image acquisition was performed in a longitudinal plane, including 5cm of the artery, located 4-5cm above the antecubital fold. Mean diameter was obtained from 3 measurements in end-diastole (end of the T wave in the electrocardiogram). Blood pressure cuff was inflated to 150mmHg (systolic pressure) for 5min and arterial diameter was registered one and five minutes after deflating. Flow mediated vasodilatation (FMV) was defined as the percentage difference between the internal diameter of the brachial artery during reactive hyperemia in the first minute and its initial diameter. Any change less than 10% was considered abnormal.

Intima-media thickness (IMT) of the left common carotid artery was evaluated. An average of three measurements from the media-adventitia interface to the adventitia-intima interface was obtained. Such measurements were performed in the longitudinal plane, 2cm before the carotid bifurcation in three different points, with biplane technique. Values were considered normal when IMT was  $\leq 0.04\text{mm}$ .

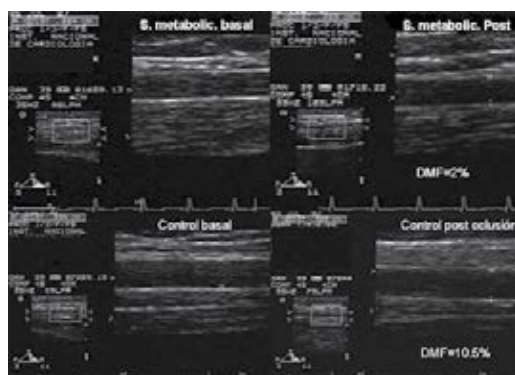
**Statistical analysis.** All variables were expressed as means and standard deviation according to their distribution. Primary objective was analyzed with a Student's T test. A  $p \leq 0.05$  was considered significant. A Pearson correlation coefficient was obtained between FMV and IMT.

## RESULTS

**Table 1** shows there was a statistically significant difference among all clinical variables between groups. Mean age for the whole sample was  $10.6 \pm 3.3$  years. Both FMV and reactive hyperemia

**Figure 1:**

Brachial artery 2D and m-mode images from a child with MS (upper images) and a healthy participant (lower images). This shows that FMV values are lower in MS group (2%), compared to control group (10.5%).



showed significant differences between children with MS vs. controls ( $p < 0.001$ ) (Figure 1). FMV values were below 10 in 73% children with MS and only in 13% of the healthy group. Children with MS had significantly higher IMT and PAP values ( $p \leq 0.001$  and  $p \leq 0.002$  respectively).

There was a negative moderate correlation between FMV and IMT ( $r = -0.562$ ).

Children with BMI of 25 to 32 kg/m<sup>2</sup> had an IMT of  $0.07 \pm 0.002$  mm vs. children with BMI  $< 25$  kg/m<sup>2</sup> ( $0.03 \pm 0.001$  mm).

## DISCUSSION

Our study results in terms of values of FMV and IMT in children with any components of the metabolic syndrome were similar to those reported in other populations.<sup>4,14-20</sup> To be noted are the low values of FMV found in the control group, which may be explained by higher altitude conditions.<sup>21</sup>

Apart from cardiovascular risk factors, other patient specific conditions may influence the IMT and FMV values, among which are: gene polymorphisms of endothelial nitric oxide synthase and other genes involved in lipid metabolism,<sup>22,23</sup> MS family history,<sup>24</sup> ethnic group,<sup>1</sup> birth weight,<sup>25</sup> mother's diet during pregnancy and lactation<sup>26</sup> and socioeconomic level.<sup>27</sup>

There's a positive correlation between IMT and age, in part due to increase in blood volume, blood pressure and body mass index.<sup>28-31</sup> Arterial hypertension is the single most important component of the MS in relation to great arteries structure and function.<sup>32</sup>

Elevated values of IMT and low values of FMV correlate with obesity, high body fat percentage,<sup>7</sup> high levels of plasma adiponectin and glucose,<sup>7</sup> glucose intolerance, hyperinsulinemia, high levels of thrombomodulin, increase in proinflammatory adhesins such as intercellular adhesion molecule 1, selectins, and C reactive protein levels,<sup>5</sup> which indicates a positive correlation between levels of systemic inflammation and endothelial dysfunction degree.<sup>5,19,33-35</sup> In our study IMT values correlate inversely with FMV.

This is the first study that shows SPAP elevation in children with MS that could be explained by vasoconstriction of the pulmonary vascular bed mediated by a reduction in nitric oxide production and endothelin 1 relative increase.

Chronic inflammation is an essential factor in MS pathophysiology. It is well known that children with MS express an increased amount of proinflammatory and antifibrinolytic factors, and thereby develop

**Table 1: Clinical and echocardiographic variables in both groups.**

Variable	MS	Controls	p
Abdominal perimeter (cm)	96.5 ± 6.7	54.2 ± 6.3	0.001
Cholesterol t (mg/dL)	181 ± 14.8	99 ± 11.7	0.000
HDL (mg/dL)	34 ± 2.9	44 ± 3.8	0.002
LDL (mg/dL)	133 ± 16.1	82 ± 14.5	0.001
Triglycerides (mg/dL)	229 ± 47.8	108 ± 15.1	0.001
Glucose (mg/dL)	144 ± 12.8	85 ± 4.5	0.001
C reactive protein (mg/L)	11.8 ± 2.2	1 ± 0.4	0.000
BMI (kg/m <sup>2</sup> )	32 ± 3.01	20 ± 3.66	0.000
FMV (%)	8.7 ± 1.6	12.9 ± 1.2	0.000
IMT (mm)	0.06 ± 0.002	0.03 ± 0.005	0.001
SPAP (mmHg)	37.8 ± 14.4	23.2 ± 5.31	0.002

HDL = high density cholesterol; LDL = low density cholesterol; BMI = body mass index.

insulin resistance which has been associated with endothelial dysfunction, the initial step in atherosclerosis.<sup>34-40</sup> Chronic inflammation represents an important factor in the origin of the MS: stimuli such as over nutrition, physical inactivity, and age, can increase the secretion of cytokines and eventually lead to an increase in insulin resistance.<sup>34,35,41-43</sup> Some authors suggest that central obesity is the trigger for glucose intolerance, increased pro-inflammatory markers, endothelial dysfunction and prothrombotic state.<sup>44</sup> Various factors secreted by adipocytes such as free fatty acids and tumor necrosis factor alpha have an important role in the development of insulin resistance by interrupting its signaling pathway.<sup>45</sup> Also, the increase in lipase activity is linked to the proinflammatory condition of the syndrome.<sup>46</sup>

IMT values decline in obese children who experience weight loss, suggesting reversibility in the atherosclerotic process.<sup>47</sup> Therefore, the importance in early detection of endothelial dysfunction in children with MS, so that an effective primary prevention strategy could be established. Exercise contributes to improving endothelial function and increasing levels of HDL-cholesterol.<sup>48</sup> Exercise during childhood exerts its protective effect on the cardiovascular system, at the endothelium level.<sup>49</sup> That is why treatment in children with metabolic syndrome should be based on changes in eating habits and rigorous exercise.

## CONCLUSIONS

Our study shows that children with MS have an increase in IMT values, higher PAP a lower VMF values compared with healthy children. All of which could represent signs of early atherosclerosis.

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