Elevated Soluble E-selectin Levels in an Infant-juvenile Population with Overweight

Abregú AV, Carrizo TR, Díaz E, Velarde MS, Prado MM, Fonio MC, Bazán MC

Department of Professional Practice, School of Biochemistry, Chemistry and Pharmacy, Nacional University of Tucumán and Endocrinology Service Hospital del Niño Jesús (SIPROSA), San Miguel de Tucumán.

ABSTRACT

Childhood overweight is associated with overweight/obesity in adulthood and it is a risk factor for diabetes and cardiovascular disease. Endothelial dysfunction is the initial stage of atherosclerosis and precedes the earliest anatomical evidence of this condition. This process is regulated by adhesion molecules located on the surface of leucocytes and endothelial cells and which would play an important role in the prediction of cardiovascular events. Among these molecules, E-selectin (E-S) is a glycoprotein that is expressed exclusively on activated endothelial cells in response to inflammatory cytokines. It has been suggested that increased levels of soluble forms of E-S (sE-S) could be specific markers of vascular endothelial damage. The aim of this study was to determine plasma levels of sE-S in overweight children and their relationship with anthropometric and biochemical variables.

Forty overweight children with an age range between 7 and 14 years, and 20 age- and gender-matched controls were studied. The inclusion criterion was a BMI > 85th percentile and below 95th percentile, for age and sex. Waist circumference (WC), BMI, Tanner stage and blood pressure were measured. Fasting blood glucose and insulin, fibrinogen (Fg), high sensitivity C-reactive protein (hsCRP), sE-S and lipid profile were measured in both groups. The data were analyzed with the SPSS 15.0 software for Windows, expressed as the median and interquartile range. Spearman’s coefficient was used to measure correlations between the studied variables. Overweight subjects had higher levels of sE-S [72.0 (50.5-92.5) vs. 24.0 (18.5-5.0) ng/ml, p =0.0001], hsCRP [1.9 (0.8-4.4) vs. 0.3 (0.2-1.1) mg/l, p =0.001], Fg [350 (315-460) vs. 247 (235-265) mg/dl, p =0.0001]. Insulin and triglycerides levels were also elevated. sE-S showed a positive correlation with WC (r=0.40, p = 002), uCRP (r = 0.58, p =0.0001) and Fg (r = 0.50, p =0.004). These results suggest the presence of endothelial activation and a pro-inflammatory state in the studied population, highlighting the importance of weight control in children for reducing cardiovascular risk in adulthood. Rev Argent Endocrinol Metab 49:119-123, 2012

The authors do not have conflicts of interest.

Key words: E-selectin, overweight, inflammation, atherosclerosis.

INTRODUCTION

Obesity is a worldwide epidemic that starts in early childhood and extends into adolescence and adulthood with a serious impact on infantile and future health. In Argentina, the prevalence of obesity in children and adolescents is similar to that observed in other countries in America, ranging between 11% and 18% (1, 2).

In the pediatric population, as in adults, central obesity is associated with cardiovascular risk factors, such as insulin resistance, dyslipidemia, presence of obesity, hypertension and type 2 diabetes (3-6). In effect, obese children and adolescents were found to have higher triglyceride levels, blood pressure and insulin resistance than their thin peers (7). In addition, overweight has been found to be related to the presence of fatty streak and low-grade stenosis in coronary arteries, which indicates that the process of atherosclerosis starts in childhood (8,9).
During recent years, it has been shown that the adipose tissue of obese individuals secretes inflammatory cytokines that induce a chronic subclinical inflammation, closely related to atherosclerosis and insulin resistance.\(^\text{(10)}\)

E-selectin (E-S) is a glycoprotein exclusively expressed on activated endothelial cells, in response to inflammatory cytokines, allowing for adhesion and migration of macrophages and leukocytes to the activated endothelium.\(^\text{(11)}\)

The presence of elevated plasma levels of soluble forms of this adhesion molecule reveals impaired endothelial function and could be an early marker of subclinical vascular inflammation.\(^\text{(12-14)}\) Several studies show that sE-S is elevated in adults with obesity, dyslipidemia, hypertension and diabetes.\(^\text{(15-20)}\) However, little research has been conducted to study this molecule in children with overweight and the number of individuals enrolled in such studies is small.\(^\text{(6,21-23)}\)

The aim of this study has been to determine plasma levels of sE-S in children and adolescents with overweight and their relationship with anthropometric and biochemical variables.

**MATERIAL AND METHODS**

We evaluated 40 patients with overweight, 18 females and 22 males, who presented at the Endocrinology Service of Hospital del Niño Jesús in San Miguel de Tucumán (Argentina) in 2009-2010, with an age range between 7 and 14 years old. Overweight was defined as a body mass index (BMI) equal to or above the 85th percentile and below the 95th percentile for age and gender. All patients enrolled in this study had normal weight at birth. For comparison, 20 age- and gender-matched healthy individuals with normal BMI constituted the control group. All patients underwent a complete clinical examination, and data on body weight, height, BMI, waist circumference, Tanner stage, blood pressure and family history of diabetes and/or cardiovascular disease were collected.

A sample of venous blood was collected from individuals in both groups after a 12-hour fast. Samples were analyzed at the laboratories of the Professional Practice Department at the School of Biochemistry of the National University of Tucumán. The following measurements were performed: fasting blood glucose (glucose oxidase method, Wiener Lab); insulin (chemiluminescence method, Siemens, USA); lipid profile: total cholesterol, HDL-cholesterol and triglycerides (enzymatic method, Wiener Lab), LDL-cholesterol was calculated with Friedewald equation, plasma fibrinogen (Clauss method, Diagnostica Stago); uCRP (Chemiluminescence assay, Immunolite 2000, Siemens) and plasma sE-S (ELISA method, R & D Systems, USA, with a sensitivity of up to 1 ng/ml and an intra-assay coefficient of variation of 4.8% and an interassay coefficient of variation of 5.7%).

Data were analyzed with the SPSS 15.0 software for Windows and expressed as median and interquartile range. Spearman’s coefficient was used to evaluate the correlations between the variables studied. A value of \(p<0.05\) was considered significant.

The study protocol was approved by the Teaching and Research Committee at Hospital del Niño Jesús. A written informed consent was signed by the parents or guardians of each child authorizing his/her participation in the study.

**RESULTS**

Table I shows the clinical characteristics and metabolic status of the children evaluated. Individuals with overweight showed elevated levels of insulin and triglycerides, with no significant differences being found in blood glucose levels or other lipid profile components in relation to the control group.
Levels of sE-S and other inflammation markers, uCRP and Fg, were significantly higher in patients with overweight (Table II). When patients with overweight were grouped according to gender and Tanner stage of pubertal development, no significant differences were found in sE-S values.

sE-S showed a positive correlation with uCRP (r = 0.58, p =0.0001) and Fg (r = 0.50, p =0.004). Table III shows the correlation between inflammation marker molecules and waist circumference, BMI, insulin and HOMA.

### TABLE I. Clinical and metabolic characteristics of the groups studied

<table>
<thead>
<tr>
<th></th>
<th>Overweight</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>40</td>
<td>20</td>
<td>--</td>
</tr>
<tr>
<td>Males / females</td>
<td>22/18</td>
<td>10/10</td>
<td>--</td>
</tr>
<tr>
<td>Chronological age (years)</td>
<td>11.3 (8-13)</td>
<td>12 (9-14)</td>
<td>NS</td>
</tr>
<tr>
<td>Tanner stage (1/2/3/4/5)</td>
<td>16/9/4/2/9</td>
<td>8/3/4/2/3</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 (25-30)</td>
<td>19 (18-21)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>91 (84-103)</td>
<td>67 (59-79)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>100 (90–110)</td>
<td>98 (88-110)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>60 (60-70)</td>
<td>60 (59-69)</td>
<td>NS</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>79 (60-85)</td>
<td>78 (68-84)</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin (uIU/ml)</td>
<td>13.0 (9.7-18.7)</td>
<td>7.2 (5.7-9.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>HOMA index</td>
<td>3.3 (1.9-6.6)</td>
<td>1.2 (0.9-1.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>165 (143-196)</td>
<td>160 (135-177)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>40 (35-44)</td>
<td>41 (35-49)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>109 (76-138)</td>
<td>94 (73-132)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>112 (90-190)</td>
<td>69 (61-84)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Results are expressed as median and interquartile range, with p < 0.05 being significant.

NS: non-significant

**DISCUSSION**

Obesity is an epidemic that starts in childhood and extends into adulthood with a serious impact on health.

Overweight/obesity is a determinant factor for the development of cardiovascular disease and type 2 diabetes. The early stage of atherosclerosis involves changes in the vascular endothelium, including but not limited to, increased expression of adhesion molecules, such as E-S, intercellular adhesion molecule-1 (ICAM-1) and the vascular cell adhesion molecule-1 (VCAM-1), which regulate the adhesive interaction between leukocytes and the endothelium (11). For this reason, these adhesion molecules are postulated as early markers or atherosclerosis (24).

Results of this study show that the levels of SE-S in a population of children and adolescents with overweight are significantly increased in relation to controls. These data are in agreement with those reported by other authors (6, 21-23) and support the evidence of early endothelial dysfunction in these individuals.

No significant differences were found in sE-S levels between males and females, in contrast to other studies, where higher levels were observed in males (6, 22). This
discrepancy might be possibly explained by the fact that those studies included a larger number of cases.

In agreement with Rao et. al, a positive correlation was found between sE-S values and abdominal obesity, but while they used the waist-to-hip ratio, we used waist circumference as measurement of abdominal obesity. This result and the findings of elevated insulin and HOMA reflect insulin resistance in the population of children and adolescents with overweight.

In this study, we also found elevated levels of uCRP and Fg, which correlated with the presence of subclinical inflammation associated with abdominal obesity in the children studied. Similar findings were reported by various authors. Even if increased levels of uCRP are related to higher rates of cardiovascular morbidity and mortality in adults, further studies are required to determine if uCRP may predict future cardiovascular events in children and adolescents.

In conclusion, these results indicate the presence of endothelial activation and subclinical inflammation, associated with abdominal obesity in the population studied. The detection of a proinflammatory state would contribute to implement an early intervention to prevent risk factors as from childhood.

**TABLE II.** Plasma levels of sE-selectin and other inflammation markers in the groups studied

<table>
<thead>
<tr>
<th>Marker</th>
<th>Overweight</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>sE-Selectin (ng/ml)</td>
<td>72.0 (50.5-92.5)</td>
<td>24.0 (18.5-35.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>uCRP (mg/L)</td>
<td>1.9 (0.8-4.4)</td>
<td>0.3 (0.2-1.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>350 (315-460)</td>
<td>247 (235-265)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Results are expressed as median and interquartile range, with p < 0.05 being significant.

**TABLE III.** Correlation between inflammation marker molecules and WC, BMI, Insulin and HOMA, in children with overweight.

<table>
<thead>
<tr>
<th>WC</th>
<th>BMI</th>
<th>Insulin</th>
<th>HOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>sE-Selectin</td>
<td>0.41*</td>
<td>0.27</td>
<td>0.45**</td>
</tr>
<tr>
<td>uCRP</td>
<td>0.36*</td>
<td>0.32*</td>
<td>0.54***</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.52**</td>
<td>0.62***</td>
<td>0.64***</td>
</tr>
</tbody>
</table>

Spearman’s coefficient: * p < 0.05, ** p < 0.01, *** p < 0.001

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REFERENCES


