

Factors Associated with Early Platelet Activation in Obese Children

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Abstract

Objective: To investigate the factors associated with platelet activation in obese children.

Design: Cross-Sectional study.

Setting: Department of Pediatrics of Regional Hospital N° 1 of Mexican Institute of Social Security in Morelia, Michoacán, Mexico.

Participants: 79 obese and 64 non obese children between 5 and 10 years.

Main Outcomes Measures: Obese children (body mass index (BMI) >85 in growth curves for CDC/National Center for Health Statistics), and the control group comprised 64 non-obese children (percentile <85), % body fat; platelet activation was assessed by sP-Selectin; other measures were Leptin; Uric Acid (UA); von Willebrand Factor(vWF), Plasminogen activator inhibitor(PAI-1), lipid profile, glucose.

Results. Obese children displayed higher plasma sP-Selectin, Leptin, PAI-1, and vWF than non-obese children. In the univariate logistic regression analysis, Leptin, vWF, UA, and HDL but not with PAI-1 were factors associated with platelet activation. By stepwise linear regression analysis adjusted by sex and age, the best predictor variables for platelet activation were Leptin (β :0.381;t:4.665;P=0.0001), vWF (β :0.211;t:2.926;P=0.004), UA (β :0.166;t:2.146;P=0.034) and HDL (β :-0.215;t:-2.819;P=0.006).

Conclusions. Obese children have a higher risk of developing early platelet activation.

Factors associated with platelet activation were Leptin, vWF, UA and HDL. Further studies involving larger number of patients over a longer duration are needed to understand the possible molecular mechanism underlying the association between Leptin, vWF, and UA

and endothelial activation and/or endothelial damage/dysfunction in obese children and its influence in cardiovascular disease in adult stage.

Keywords: Leptin; Uric acid; Endothelial activation; Obesity; Children.

INTRODUCTION

Childhood obesity is a public health problem in Mexico and in the worldwide because of the later clinical consequences, including diabetes mellitus, hypertension, and cardiovascular disease (CVD) [1]. The rapid increase in the prevalence and severity of obesity in children is likely to lower the age of onset and increase the incidence of CVD. **Childhood obesity is associated with endothelial dysfunction one of the earliest changes in the development of atherosclerosis [2,3], and evidences support that atherosclerotic cardiovascular disease beginning in childhood [4]; Additionally, the high serum levels of LDL-cholesterol and total cholesterol in childhood, were associated in adults with the carotid intima-media thickness [5] and subclinical atherosclerosis [6].** In adults, inflammation, endothelial dysfunction, and hyperuricemia are factors that contribute to a link between obesity and CVD. Leptin has been shown to represent an important candidate to link these disorders [7,8] because of their potential role in the regulated functioning the immune system [9], on platelet activation and segregation [10], and on relation with uric acid [11].

In presence of obesity, inflammation leads to platelets activation and increased plasma levels of prothrombotic proteins stored in platelet α -granules including: Soluble P-Selectin (sP-Selectin), von Willebrand Factor (vWF), and Plasminogen activator inhibitor-1 (PAI-1). **High levels of these proteins are believed to play a central role in accelerating the risk of atherothrombosis.** [12]. sP-Selectin is not only expressed on activated endothelial cells but also on activated platelets and it mediates rosetting of the platelets with monocytes and neutrophils that contribute to atherosclerotic lesion [13], so is considered as a plasma marker of platelet activation **and endothelial dysfunction** in the atherogenic process that

has been related to adverse cardiovascular events in adults [14,15]. vWF levels have been significantly associated with insulin resistance (IR) [16]. Increased PAI-1 levels have been associated with risk of thrombosis and fibrosis, and PAI-1 has been shown to have a direct effect in the development of IR and type 2 diabetes [17].

Disorders of uric acid (UA) metabolism are often seen in conjunction with factors associated with lifestyles such as an unbalanced diet abundant in purine, obesity, and alcohol consumption [18]. In adolescents, UA levels are significantly increased in obesity [19], and some studies suggests that UA stimulates vascular inflammation and endothelial dysfunction **and it predicts adult blood pressure** [20-22].

The aim of our study was to investigate the factors associated with platelet activation in obese children

Methods

Participants

Between March 2009 and February 2010, a cross-sectional study was carried out in 143 children of both sexes from whom demographic and clinical data were collected. At the time of the study, the children were aged between 5 and 10 years. One group comprised 79 obese children (body mass index (BMI) over percentile 85 in growth curves for CDC/National Center for Health Statistics), and the other (control group) comprised 64 non-obese children (percentile <85). Children were consecutively enrolled at the Department of Pediatrics of Regional Hospital N° 1 of Mexican Institute of Social Security in Morelia, Michoacán, Mexico. Children with primary hyperlipidemia, hypertension, diabetes or glucose intolerance were excluded from both the test group and the control

group, as were children with secondary obesity. Any child receiving pharmacological treatment was also excluded. All parents gave their written consent and children gave their verbal and written assent, and the study was authorized by the Hospital Ethical Research Committee.

Anthropometric measurements and blood pressure.

Weight was measured to nearest 0.1 kg and height to nearest 0.1 cm. BMI was calculated as weight (kg)/height (m²), percentage body fat was assessed by bioelectrical impedance [23] **and Body Surface Area (BSA) were calculated with Haycock formula [24].** Blood pressure was measured with a mercury sphygmomanometer after 20 min rest, in a supine position. Three sizes of cuff were used (9x21, 11x36 and 12x41 cm); the cuff width was required to cover 2/3 of the length of the child's arm.

Blood sampling

Blood samples **of all children** were collected after 12 h fasting from a vein in the antecubital fossa, without venous occlusion. **Before collecting the blood, we asked at parents each child the hour of last food for fasting confirming.** Blood samples were separated into aliquots and frozen immediately at -70°C until analysis to avoid inter-assay variability.

Glucose, UA, cholesterol, triglycerides (TG), and HDL, **and** LDL concentrations were measured using an automatic analyzer (Roche Diagnostics, Mannheim, Germany). Blood count was realized in hematologic analyzer Nihon Kohdem (Nihon Kohdem Corporation, Japan). Leptin and sP-Selectin were realized by an enzyme immunoassay (Invitrogen Corporation, CA, USA). vWF:Ag was determined by ELISA (Immubind®, American

diagnostica, USA). PAI-1 was determined by ELISA (Prepro-Tech Inc, USA). **In all determinations, the intra-and inter-assay variability were less than 5%.** A value of sP-Selectin ≥ 44.32 ng/mL (third quartile) was cut-off point considered for analyzing platelet activation.

Statistical analysis

Data were stored and analyzed using SPSS 18.0 statistical package (SPSS Inc, Chicago, IL). Test selection was based on evaluating the variables for normal distribution using the Kolmogorov-Smirnov test. Differences between groups were calculated using a Student's t-test for independent samples. Pearson's correlation and linear regression coefficients were used to analyze the relation between variables. The independence of association of leptin with platelet activation was assessed by logistic regression analysis (when dependent variable, i.e., platelet activation [sP-Selectin] was entered as a categorical variable stratifying into two groups according to the 75 percentile observed (44.32 ng/mL).

Univariate linear regression analyses and stepwise regression models were used to test the predictive association of biochemical parameters (Leptin, PAI-1, vWF, UA, glucose, cholesterol, triglycerides, LDL, HDL and, PAI-1) with platelet activation. A $P < 0.05$ was considered statistically significant in all cases.

Results

Demographic, Clinical and Biochemical characteristics of all participants in the study are presented in table 1. Obese children displayed higher plasma concentrations of sP-Selectin,

Leptin, PAI-1, vWF and serum UA levels than non-obese children. **Similarly**, obese children had higher values of systolic and diastolic blood pressure than non-obese children. Correlations of Leptin, vWF and UA with platelet activation (sP-Selectin) are showed in figure 1. **Correlations between BMI, % Body fat and BSA with sP-Selectin are showed in figure 2.** Subsequently, Leptin levels correlated positively with BMI ($r=0.535$; $P=0.0001$), % body fat content ($r=0.541$; $P=0.0001$), triglycerides ($r=0.317$; $P=0.0001$), UA ($r=0.343$; $P=0.0001$) and negatively with HDL ($r=-0.211$; $P=0.011$).

In the stepwise linear regression analysis, the best **predictor** variables for platelet activation were Leptin ($\beta:0.395$; IC95% 0.229-0.561; $t:4.697$; $P=0.0001$), vWF ($\beta:0.211$; IC95% 0.148-0.441; $t:2.926$; $P=0.004$), UA ($\beta:0.208$; IC95%0.129-0.561; $t:2.477$; $P=0.014$) and HDL ($\beta:-0.215$; IC95% -0.402-0.561; $t:-2.819$; $P=0.006$). Serum glucose, cholesterol, LDL, body fat and waist circumference were **non-predictor** variables for platelet activation.

Finally, **figure 3** shows the relative risk and its confidence interval 95% adjusted by sex and age. Leptin, vWF, UA, and HDL but not with PAI-1 were **risk** factors associated with platelet activation.

DISCUSSION

The results of this study support that high circulating levels of sP-Selectin, Leptin, PAI-1, vWF and UA in childhood obesity are related to the presence of platelet activation, and may promote early vascular abnormalities potentially responsible for increased cardiovascular morbidity and mortality later in life. In addition, adipose tissue accumulation probably represents the main risk factor responsible for platelet

size, activation of vascular endothelium and release of prothrombotic proteins in obese children [25]. Notably, so Leptin, vWF, and UA were independent risk factors in the platelet activation.

The involvement of Leptin in increased platelet activation in human obesity is not universally accepted, since several studies [25-27] provided conflicting results about platelet responsiveness to Leptin in overweight and obesity in adults. **Likewise Fochini et al** [10], we confirm that obese children have higher Leptin and platelet concentrations in comparison with non-obese children, so this increase could favor early functional alterations and represent higher risk for **developing early atherosclerosis and CVD**. A possible mechanism can be related with adenosine concentration (ADO) as endogenous mediator released from platelets storage granules [28] and studies in vitro showed that Leptin synergizes with subthreshold concentrations of agonist such as ADO to induce platelet aggregation [29]. In this context, Elbatarny and Maurice [30] have reported that Leptin-induced platelet activation via activation of PDE3A may represent a molecular basis for the association between hyperleptinemia and cardiovascular disease. However, more studies are needed to confirm this molecular mechanism in children.

In adults, obesity is associated with higher levels of circulating endothelial dysfunction biomarkers such sICAM-1 and vWF [31]. In our study, sICAM-1 was **not** quantified but vWF was higher in obese children. We found an association between vWF and sP-Selectin. However, it is reasonable to assume the probability of early endothelial damage additionally to platelet activation and proinflammatory effect of Leptin in obese children.

Equally important, we found an association between UA and sP-Selectin. The relationship between UA and endothelial activation (sP-Selectin) is consistent with the prooxidative effect and proatherogenic properties of UA including endothelial cell activation, platelet activation, and increased platelet adhesiveness [32]. The role of UA as an additional risk factor for developing endothelial dysfunction and smooth muscle cell proliferation is caused by an excessive activity of xantine oxidase enzyme by degraded purine metabolism and formation of reactive oxygen and nitrogen species that **lead** to oxidative stress and later to develop endothelial dysfunction [33].

Bedir et al [11] showed that serum Leptin level was independently associated with UA only in overweight and obese adults. Our results about the correlation between Leptin and UA in obese children are consistent with the proposal by Bedir that Leptin appears to be a good candidate for the missing link between obesity and hyperuricemia.

In this study, triglycerides and HDL were higher in obese children but only HDL was a predictor factor by platelet activation. The Bogalusa study [34] showed that in overweight 5-to 10-year old children had two or more cardiovascular risks factors (hypertriglyceridemia, high LDL and, low HDL) that would substantially increase the risk for earlier cardiovascular disease. Likewise, recently we and others have reported that low levels of HDL are associated with metabolic syndrome and cardiovascular risk in Mexican Children [35-37]. From our knowledge, this is the first report of early platelet activation in Mexican obese children. Finally, we found in this study that obese children had values higher blood pressure than non-obese; hence **a higher blood pressure could induce endothelial activation. Obesity and high blood pressure are** suggested as risks factor for

early development of hypertension in this population. In fact, this was previously reported by us in children of parents with diabetes mellitus or arterial hypertension [35].

This study presents some limitations. First, the study is of cross-sectional nature, and in the absence of a prospective longitudinal analysis, interpretation of the correlations can only be inferred. Second, the information about lifestyles of the children is limited. The habit of frequently eating purine-rich food or fruit juice may cause increasing Leptin and UA levels. Mexican dietary intake (carbohydrates, lipids and proteins) with the food frequency by standard portion sizes for each food are necessary to evaluate in obese children.

Conclusion.

Obese children **present early** presence of platelet activation, and Leptin, vWF, UA and HDL were factors associated with platelet activation. In the **practical medical field** we need to do the early detection of risk factors for CVD in children. Further studies involving larger number of patients over a longer duration are needed to understand the possible clinical and molecular mechanism underlying the association between Leptin, vWF, and UA and endothelial activation and/or endothelial damage/dysfunction in obese children and its implications in CVD in adult life.

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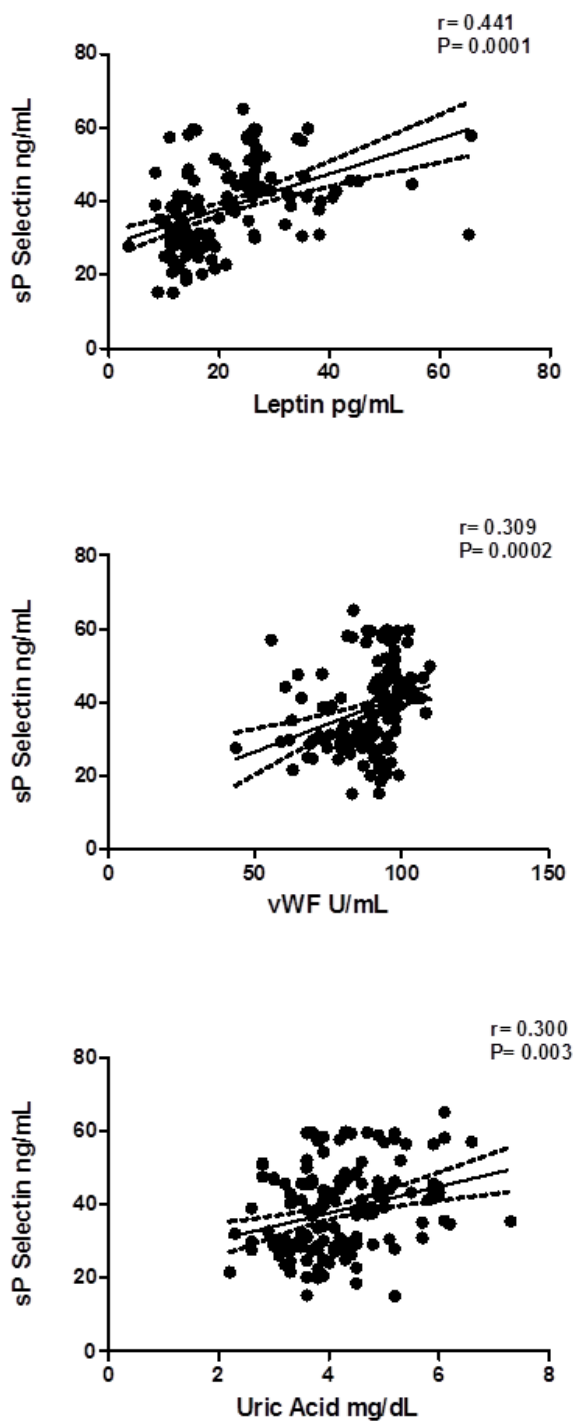
Table 1. Clinical and biochemical variables of obese and non-obese children.

Variables	Obese n= 79	Non-obese n= 64	P
Age, yr	7.44 ± 1.44	7.20 ± 1.26	0.411
Male/female, n	50/29	37/27	
BMI, kg/m ²	21.77 ± 2.84	15.83 ± 0.96	0.0001
Body fat content, %	31.56 ± 6.37	18.06 ± 3.61	0.0001
Body surface area, m²	1.22 ± 0.25	0.91 ± 0.12	0.0001
sBP, mmHg	96.64 ± 9.42	88.67 ± 7.35	0.0001
dBp, mmHg	58.03 ± 8.29	51.40 ± 4.91	0.0001
Haemoglobin, g/dL	14.71 ± 0.74	14.20 ± 0.85	0.019
Platelets, x10 ³ cells/μL	362.35 ± 71.15	326.79 ± 55.27	0.014
Glucose, mg/dL	88.97 ± 6.23	87.60 ± 6.48	0.203
Uric Acid, mg/dL	4.51 ± 0.95	3.81 ± 0.78	0.0001
Total Cholesterol, mg/dL	170.64 ± 28.58	165.97 ± 31.74	0.357
Triglycerides, mg/dL	115.48 ± 57.12	77.11 ± 27.81	0.0001
HDL, mg/dL	44.66 ± 10.62	50.95 ± 10.31	0.001
LDL, mg/dL	102.59 ± 25.81	100.51 ± 29.84	0.655
Leptin , pg/mL	26.77 ± 10.66	14.35 ± 4.18	0.0001
PAI-1, pg/mL	64.18 ± 30.49	43.24 ± 18.06	0.0001
vWF, U/mL	93.19 ± 9.70	83.55 ± 11.57	0.0001
sP-Selectin, ng/mL	45.65 ± 9.01	29.39 ± 6.40	0.0001

Data are expressed as mean ± SD. BMI: Body mass index; sBP: systolic blood pressure; dBp: diastolic blood pressure; HDL: High density lipoproteins; LDL: low density lipoproteins; PAI-1: Plasminogen activator inhibitor-1; vWF: von Willebrand Factor.

t-Student test *P*<0.05

Legends Figure

Figure 1. Univariate correlations between sP-Selectin and Leptin, vWF, uric acid in obese children.

vWF: von Willebrand Factor

Figure 2. Univariate correlations between sP Selectin and Body Mass Index, % Body Fat and Body Surface Area in obese children.

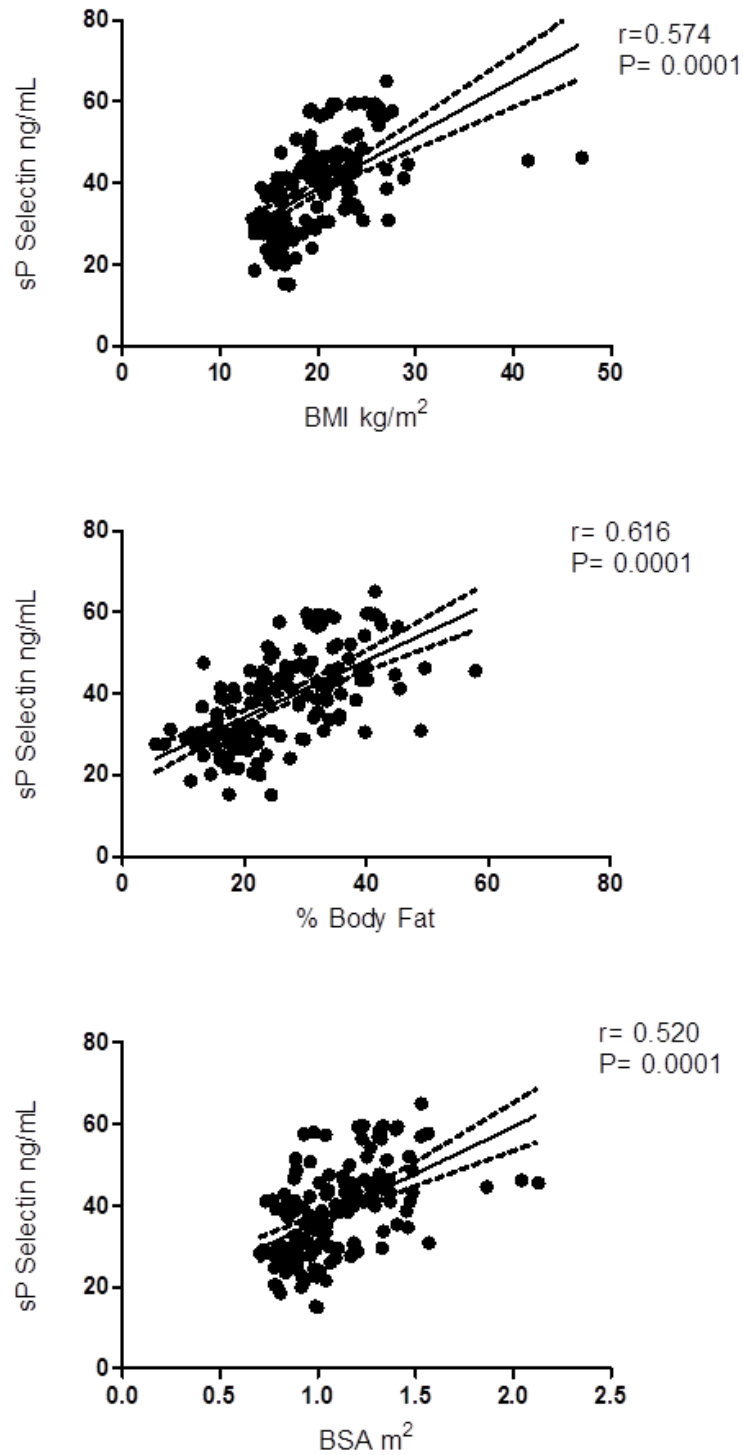


Figure 3. Relative risk analysis between platelet activation (sP-Selectin, as dependent variable) and Leptin, vWF, PAI-1, uric acid and HDL in obese children.

PAI-1: Plasminogen activator inhibitor-1; vWF: von Willebrand Factor; HDL: High density lipoproteins.

