Relationship between serum leptin levels and sodium excretion in a local population of obese children and adolescents

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ABSTRACT

Obesity is associated with elevated levels of leptin and most obese individuals are “selectively” resistant to its metabolic action, without appetite loss or increased energy expenditure, with preservation and stimulation of the activation of the sympathetic system at both the central and peripheral cardiovascular and renal levels. These mechanisms could modify the regulation of sodium metabolism in the kidney.

Objective: To determine whether there is any correlation between serum leptin levels and urinary sodium excretion in a population of obese children and adolescents.

Material and methods: 190 children and adolescents between 5 and 15 years of age were studied: 125 with body mass index (BMI) ≥ 95 percentile constituted the obese group (OB) and 65 with BMI percentile 5 - < 85 the control group (C). Concentrations of serum sodium (Na) and urinary sodium (Nao) were measured with ion selective electrode; serum leptin levels were measured by the immunoradiometric method.

Results: Differences between groups were significantly lower for urinary sodium values (mEq/kg/day) in obese subjects compared with controls for both sexes and in different age groups. The obese population has higher leptin/BMI (ng/ml/IMC) and lower concentrations of urinary sodium in the different groups/subgroups: OB girls 5 to 9 years of age Nao 2.69 ± 0.19, leptin/BMI 0.63 ± 0.06; OB girls 10 to 15 years Nao 2.20 ± 0.17, leptin/BMI 1.11± 0.12; OB boys 5 to 9 years Nao 2.07± 0.16, leptin/BMI 0.80 ± 0.15; OB boys 10 to 15 years Nao 2.57 ± 0.23, leptin/BMI 0.65 ± 0.09.

Our study suggests that elevated serum leptin levels, typical of conditions such as obesity, may contribute to alterations in sodium metabolism, due to decreased urinary excretion of this ion.

No financial conflicts of interest exist.

Key words: leptin, sodium excretion, obesity, children and adolescents

INTRODUCTION

Obesity is a disease, defined as such by the WHO in 1997 (1), characterized by an increase in body fat. It usually develops in childhood and adolescence, and it is defined as the presence of excess adipose tissue accumulation as a result of chronic positive energy balance, due to an imbalance between food intake and energy expenditure (2,3).

Various studies state that in a high percentage of obese children and adolescents, obesity is likely to persist into adult life (4, 5), associated with a high risk of developing cardiovascular and metabolic diseases such as: coronary artery disease, hypertension, type 2 diabetes mellitus and dyslipidemia (6,7).

Factors currently known to be involved in body fat mass regulation include leptin, the protein product of the ob gene, discovered in 1994 (6, 8-10). This hormone, synthesized and secreted by adipose tissue was initially described by its actions in the central nervous system, mainly in the hypothalamus, suppressing appetite and stimulating energy expenditure, and consequently reducing adipose tissue mass and body weight (6, 7, 9,11-15). In the past decade, substantial evidence has suggested that in physiological conditions, and through both direct and indirect mechanisms, leptin may play an important role in cardiovascular and renal functions through a pressor effect (sympathetic activation) and depressor action (increased endothelial nitric oxide, natriuresis and angiogenesis), with the latter effect being predominant (6-9, 13, 15-25).

Obesity is associated with elevated blood leptin levels and most obese individuals have “selective” resistance to the metabolic action of leptin, with no decrease in appetite or
increase in energy expenditure, with preservation and stimulation of the activation of the sympathetic system at both the central and peripheral cardiovascular and renal levels (6, 7, 9, 13, 15, 24, 26-32).

Hyperleptinemia is currently implicated in the association between obesity and hypertension and in the development of cardiovascular and renal diseases through mechanisms such as: increased sympathetic nervous system activation, endothelial dysfunction (nitric oxide deficit), vasoconstriction and impaired regulation of sodium metabolism at renal level (6, 7, 15, 19, 23, 24, 32-36).

Given the evidence gathered and the lack of information on leptin and its relationship with sodium homeostasis in the pediatric population, we decided to investigate if there is any correlation between serum leptin levels and urinary sodium excretion in a population of obese children and adolescents.

**MATERIAL AND METHODS**

This cross-sectional study included 125 obese children and adolescents of both genders with an age range between 5 and 15 years old, considering 10 years of age as the cut-off point between childhood and adolescence - WHO (37), who attended the Nutrition Sector of the Outpatient Office at the provincial children’s hospital Dr. F. Barreyro (Posadas, Misiones, Argentina) during 2007-2008.

Subjects with endocrine, renal or genetic disorders or who were taking medication that may alter body weight, blood pressure and/or electrolyte excretion were excluded.

A control group was created including 65 eutrophic children and adolescents of both genders with an age range between 5 and 15 years old, who attended the aforementioned office to obtain their certificate of good health during the same period.

The study protocol was approved by the Hospital Ethics Committee. All parents or guardians signed an informed consent form after the study had been explained to them and before the initiation of the study, in accordance with the ethical principles stated in the Declaration of Helsinki (38).

Blood pressure and the following anthropometric variables were measured: weight, height and body mass index (BMI). Hypertension is defined as average systolic and/or diastolic blood pressure that is 95th percentile for gender, age, and height on 3 or more separate occasions (39).

The BMI was calculated as weight (kg)/height² (m). Eutrophic and obese populations were defined according to BMI between the 5th and 85th percentiles and BMI ≥ 95th percentile, respectively (40).

Blood samples were obtained after a 12-hour fast. All study participants collected 24-h urine samples.

The following measurements were performed: blood glucose by the GOD-POD enzymatic-colorimetric method of Trinder – Coefficient of variation (CV) 6.76% (Wiener), serum and urine creatinine by colorimetric-kinetic method - CV 8.5% (Boheringer). Readings were performed with BTS 320 spectrophotometer (Biosystems). Serum and urine sodium concentrations were measured by ion-selective electrode (ISE), Easy Lyte Plus – Médica, CV 2.4%. Serum leptin levels were measured in duplicate by immunoradiometric assay (IRMA) DSL -23100; the assay sensitivity was 0.10 ng/ml – CV 7.2%. Readings were performed using an Ingetron MN 2000-E manual well counter.

Estimate endogenous creatinine clearance (CrCl) was used as an indicator of glomerular filtration rate: urine creat. x 24-hour urine collection x 1.73/ serum creat. x body surface area.
Two types of controls were assayed: an in-house control, Standatrol (Wiener) and an external control, by affiliation with the External Quality Assessment Program (PEEC) of the Argentine Biochemistry Foundation. Leptin quality control was commercially supplied.

Quantitative variables were tested for normality using the Shapiro-Wilks test. The Student t test was used to compare normal distributions and the Mann-Whitney non-parametric test was used for not normally distributed variables. Data are expressed as mean ± SD and their distribution range. Associations were evaluated with Pearson’s and Spearman’s correlation analyses. A 95% confidence interval was used as the level of statistical significance. The statistical analysis was performed using the Statgraphical 5.1 software (41, 42).

RESULTS

Characteristics of the participants at baseline: 190 children were enrolled in the study. According to nutritional status, 65 (34 %) were eutrophic (C) and 125 (66%) were obese (OB). Females were 34 (52%) in the control group and 72 (58%) in the group of obese subjects. The male population included 31 (48%) controls and 53 (42%) obese subjects.

TABLE I. Basal characteristics of study participants.

<table>
<thead>
<tr>
<th>Variables</th>
<th>C n = 65</th>
<th>OB n = 125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years</td>
<td>10 ± 0.3</td>
<td>10 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>(6 – 15 )</td>
<td>(4 – 14)</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>34/31</td>
<td>72/53</td>
</tr>
<tr>
<td>BMI kg/m</td>
<td>17.0 ± 0.3</td>
<td>26.4 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>(10.2 – 21.8)</td>
<td>(17.5 – 42.0)*</td>
</tr>
<tr>
<td>SBP mmHg</td>
<td>97 ± 1</td>
<td>106 ± 1</td>
</tr>
<tr>
<td></td>
<td>(70 – 120)</td>
<td>(70 – 150)*</td>
</tr>
<tr>
<td>DBP mmHg</td>
<td>57 ± 1</td>
<td>64 ± 1</td>
</tr>
<tr>
<td></td>
<td>(40 – 80)</td>
<td>(30 – 95)*</td>
</tr>
<tr>
<td>Blood glucose mg/dL</td>
<td>86 ± 1</td>
<td>86 ± 1</td>
</tr>
<tr>
<td></td>
<td>(69 – 106)</td>
<td>(60 – 117)</td>
</tr>
<tr>
<td>CrCl ml/min/BSA</td>
<td>118 ± 5</td>
<td>123 ± 4</td>
</tr>
<tr>
<td></td>
<td>(61 – 287)</td>
<td>(49 – 272)</td>
</tr>
<tr>
<td>sNA mEq/l</td>
<td>140 ± 0.3</td>
<td>140 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>(136 – 147)</td>
<td>(130 – 151)</td>
</tr>
<tr>
<td>uNA mEq/l</td>
<td>3.77 ± 0.20</td>
<td>2.37 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>(0.98 – 7.93)</td>
<td>(0.34 – 6.14)*</td>
</tr>
<tr>
<td>Leptin ng/ml</td>
<td>6.04 ± 0.65</td>
<td>24.17 ± 2.10</td>
</tr>
<tr>
<td></td>
<td>(0.32 – 20.0)</td>
<td>(1.00 – 121.0)*</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD (range); * p < 0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; CrCl: glomerular filtration rate; sNA: serum sodium, uNA: urine sodium; BSA: body surface area

Even if no hypertensive subject was identified, the obese population was found to have significantly higher systolic and diastolic blood pressure values than the control
population (p < 0.001). This group had serum and urine sodium concentrations, and glomerular filtration rates within normal ranges. No significant differences were found in blood glucose levels (p = 0.728), glomerular filtration (p = 0.699) and serum sodium concentrations (p = 0.778) when compared between both groups.

A significant decrease was observed in sodium urinary excretion (p < 0.001) and significantly higher circulating leptin levels (p < 0.001) in the obese population, when compared to controls (Table I).

As there is no consensus on reference ranges for circulating leptin in children and there are no reference ranges in our population, the 90th percentile is estimated as cut-off point. Percentile distribution of serum leptin levels in study children and adolescents according to nutritional status showed that in eutrophic subjects, the 90th percentile corresponded to a concentration of 14.50 ng/ml, while in obese subjects, it corresponded to 54.00 ng/ml.

Spearman correlation demonstrated a significant association between leptin and age only for females, both in obese subjects (r = 0.40, p = 0.0007) and in controls (r = 0.72, p = 0.00001). No correlations were found for males, neither in obese subjects (r = 0.08, p = 0.567) nor in controls (r = 0.17; p = 0.3420). Figure 1.

To determine the relationship between circulating leptin and BMI, serum leptin concentrations were correlated with the corresponding BMI in the various groups/subgroups. A significant correlation was found between circulating leptin values and BMI in obese individuals (females: r = 0.40, p = 0.0007; males: r = 0.50, p = 0.0003) and controls (females: r = 0.65, p = 0.0002; males: r = 0.37, p = 0.0442). Figure 2.

Given the direct correlation existing between circulating leptin levels and BMI, the leptin/BMI ratio was calculated. The leptin/BMI ratio levels obtained for the obese population (0.84 ± 0.06; range: 0.04 – 3.47) are significantly higher than those found for the control group (0.34 ± 0.04; range: 0.02 – 1.21) when both groups are compared.

The percentile distribution of the leptin/BMI ratio in study children and adolescents according to nutritional status showed that in eutrophic subjects, the 90th percentile corresponded to a concentration of 0.86 ng/ml/BMI, while in obese subjects, it corresponded to 1.74 ng/ml/BMI.

Table II shows the leptin/BMI ratio values in children and adolescents according to gender and two age groups (5 to 9 and 10 to 15 yr.) for controls and obese subjects. When comparing leptin/BMI values, significantly higher differences were found in the obese population vs. controls (p<0.005), for females and males.

Comparison of these values by age group showed significant differences for females, which were greater in both obese and control adolescents (p<0.005); this difference by age group was not found in males (p >0.05).

Significant gender differences were found between obese and control adolescents of both genders (p <0.005), being greater in females; this gender difference was not found in the age group from 5 to 9 years (p >0.05).

As shown in Tables III and IV, significantly lower differences were found in urine sodium values in the obese population vs. controls, for both genders in the various age groups (p<0.005; girls 5 to 9 yr. p < 0.05). No significant differences were found for serum sodium (p>0.05).

Even if there is no correlation between leptin values and natriuresis, the obese population has higher leptin/BMI values for lower concentrations of urine sodium (p = 0.390; r = -0.0772).
Figure 1. Correlation between circulating concentrations of leptin and age: obese girls (A), control girls (B), obese boys (C), control boys (D).

**FALTA CAMBIAR COMAS POR PUNTOS EN LAS CIFRAS DE LOS GRÁFICOS**
Figure 2. Correlation between circulating concentrations of leptin and BMI: obese girls (A), control girls (B), obese boys (C), control boys (D).

TABLE II. Serum levels of leptin/BMI in control (C) and obese (OB) children and adolescents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 to 9 years</td>
<td>10 to 15 years</td>
</tr>
<tr>
<td>Leptin/BMI</td>
<td>n = 13</td>
<td>n = 21</td>
</tr>
<tr>
<td>ng/ml/BMI – C</td>
<td>0.14 ± 0.09</td>
<td>0.51 ± 0.06**</td>
</tr>
<tr>
<td></td>
<td>(0.04 – 1.21)</td>
<td>(0.17 – 0.98)</td>
</tr>
<tr>
<td>Leptin/BMI</td>
<td>n = 25</td>
<td>n = 47</td>
</tr>
<tr>
<td>ng/ml/BMI – OB</td>
<td>0.63 ± 0.06*</td>
<td>1.11 ± 0.12* and **</td>
</tr>
<tr>
<td></td>
<td>(0.30 – 1.58)</td>
<td>(0.10 – 3.47)</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD (range); *p < 0.005 OB vs. C; **p < 0.005 females; adolescents vs. 5 to 9 years, in OB/C; § p < 0.005 female adolescents vs. male adolescents, in OB/C.
TABLE III. Serum Na, urine Na and leptin/BMI values in control (C) and obese (OB) children, females

<table>
<thead>
<tr>
<th>Variable</th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>5 to 9 years</td>
<td>10 to 15 years</td>
<td>5 to 9 years</td>
<td>10 to 15 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>OB</td>
<td>C</td>
<td>OB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 13</td>
<td>n = 25</td>
<td>n = 21</td>
<td>n = 47</td>
<td></td>
</tr>
<tr>
<td>sNa mEq/l</td>
<td>140 ± 0.9</td>
<td>138 ± 0.8</td>
<td>140 ± 0.5</td>
<td>140 ± 0.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(136 – 147)</td>
<td>(131 – 149)</td>
<td>(137 – 147)</td>
<td>(131 – 151)</td>
<td></td>
</tr>
<tr>
<td>uNa mEq/Kg/day</td>
<td>3.72 ± 0.58</td>
<td>2.69 ± 0.19*</td>
<td>3.52 ± 0.35</td>
<td>2.20 ± 0.17**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.98 – 7.93)</td>
<td>(0.83 – 4.97)</td>
<td>(1.34 – 6.38)</td>
<td>(0.65 – 6.14)</td>
<td></td>
</tr>
<tr>
<td>Leptin/BMI</td>
<td>0.14 ± 0.09</td>
<td>0.63 ± 0.06**</td>
<td>0.51 ± 0.06</td>
<td>1.11 ± 0.12**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.04 – 1.21)</td>
<td>(0.30 - 1.58)</td>
<td>(0.17 – 0.98)</td>
<td>(0.10 – 3.47)</td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD (range), *p < 0.05 OB vs. C; **p < 0.005 OB vs. C.

TABLE IV. Serum Na, urine Na and leptin/BMI values in control (C) and obese (OB) children, males

<table>
<thead>
<tr>
<th>Variable</th>
<th>Males</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 to 9 years</td>
<td>10 to 15 years</td>
<td>5 to 9 years</td>
<td>10 to 15 years</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>OB</td>
<td>C</td>
<td>OB</td>
</tr>
<tr>
<td></td>
<td>n = 12</td>
<td>n = 21</td>
<td>n = 19</td>
<td>n = 32</td>
</tr>
<tr>
<td>sNa mEq/l</td>
<td>140 ± 0.6</td>
<td>140 ± 1.0</td>
<td>140 ± 0.4</td>
<td>140 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>(137 – 144)</td>
<td>(130 – 149)</td>
<td>(137 – 144)</td>
<td>(134 – 144)</td>
</tr>
<tr>
<td>uNa mEq/Kg/day</td>
<td>4.63 ± 0.44</td>
<td>2.07 ± 0.16</td>
<td>3.53 ± 0.30</td>
<td>2.57 ± 0.23</td>
</tr>
<tr>
<td></td>
<td>(1.61 – 7.06)</td>
<td>(0.80 – 3.56)**</td>
<td>(1.48 – 6.14)</td>
<td>(0.34 – 5.73)*</td>
</tr>
<tr>
<td>Leptin/BMI</td>
<td>0.27 ± 0.15</td>
<td>0.80 ± 0.15**</td>
<td>0.27 ± 0.05</td>
<td>0.65 ± 0.09**</td>
</tr>
<tr>
<td></td>
<td>(0.02 – 0.79)</td>
<td>(0.12 – 2.31)</td>
<td>(0.02 – 0.87)</td>
<td>(0.04 – 2.62)</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD (range), *p < 0.05 OB vs. C; **p < 0.005 OB vs. C.

DISCUSSION

This study provides relevant data on the relationship between serum leptin levels and sodium homeostasis in the pediatric population.

In normal adolescents, gender differences have been reported, with sexual dimorphism, as regards serum leptin levels (higher concentrations in females than in males) which could be explained, at least in part, by the stimulating effect of estrogens for girls and the suppressing effect of androgens for males. Furthermore, the presence of a larger amount of body and subcutaneous fat in adolescent females contributes to higher levels of circulating leptin in this population (13, 43-46). Thus, in our study, when comparing serum leptin levels by age in eutrophic children and adolescents, significantly higher differences were found in females but not in males. This was also observed in obese subjects; in both groups leptin showed a positive association with age only in girls. Several investigators (10, 13, 14, 29, 30, 43, 46, 47) have reported higher serum leptin levels in obese subjects and their correlation with body mass index, one of the anthropometric variables indicative of the fat component, and these reports are consistent with our findings. Obese subjects at all ages, from the neonatal period to old age, have higher leptin levels than eutrophic subjects (13, 43). These differences persist even when circulating leptin concentrations are adjusted by body mass index.

Several years ago, the concept of selective insulin resistance was introduced, whereby a restricted resistance to the metabolic effects on glucose uptake, with preservation of
the sympathoexcitatory actions, explains the association of insulin resistance, hyperinsulinemia, dyslipidemia and hypertension (48, 49). It is speculated that the concept of selective leptin resistance (decreased food intake and increased energy expenditure with preservation of cardiovascular and renal effects) might have similar implications in the association between hypertension and obesity (15,24, 26,50, 51).

Chronic hyperleptinemia, typical in different phenotypes of obesity, is associated with an increased activation of the sympathetic nervous system, which at renal level generates vasoconstriction and increased sodium reabsorption along the nephron; furthermore, systemic and renal nitric oxide deficiency leads to a decrease in vasodilation and natriuresis (24,50,52,53).

Renal retention of sodium would be related to increased Na-K-ATPase activity, which would increase tubular sodium reabsorption, mainly at the level of the renal medulla (6, 24, 53). This decrease in natriuresis could not be attributed to changes in glomerular filtration or low sodium intake (24).

The antinatriuretic action of leptin in obese individuals has been reported by several studies (6, 7, 19, 24, 32, 50, 52, 53) and our results are consistent with these observations; furthermore, data obtained from this study suggest that obese subjects have higher values of circulating leptin levels and leptin/BMI ratio, for lower urine sodium concentrations.

To sum up, leptin has many actions that may be important not only for energy metabolism but also for cardiovascular and renal regulation under physiologic and pathophysiologic conditions.

Our results suggest that elevated serum leptin levels, typical of conditions such as obesity, may contribute to alterations in sodium metabolism, due to decreased urinary excretion of this ion.

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