Decrease in leptin production by the adipose tissue in obesity associated with severe metabolic syndrome

Diminuição da produção de leptina pelo tecido adiposo na obesidade associada à síndrome metabólica severa

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ABSTRACT

Objective: To evaluate the associations between leptinemia and the components of metabolic syndrome (MetS).

Methods: Fifty-one obese adults (9 men; 36.7 ± 10.0 years; body mass index (BMI) 46.2 ± 10.0 kg/m²) were submitted to clinical examination, determinations of body fat mass (BF; bioimpedance) and resting energy expenditure (REE, indirect calorimetry), and to hormonal and biochemical analysis. Patients were categorized into three groups, according to the number of criteria for MetS: Group I: none or 1; Group II: 2; and Group III: 3 or 4 criteria.

Results: Absolute leptinemia (LepA; 37.5 ± 16.9 ng/mL) was directly correlated with BMI (r = 0.48; p = 0.0004), waist circumference (r = 0.31; p = 0.028) and BF (r = 0.52; p = 0.0001). Leptinemia adjusted for BF (LepBF) was inversely correlated with weight (r = -0.41; p=0.027), REE (r = -0.34; p = 0.01) and number of MetS criteria (r = -0.32; p = 0.02). There was no difference in LepA among the groups. LepBF in Group III (0.58 ± 0.27 ng/mL/kg) was significantly lower compared to Group I (0.81 ± 0.22 ng/mL/kg; p = 0.03) and Group II (0.79 ± 0.30 ng/mL/kg; p = 0.02).

Conclusions: Leptin production by the adipose tissue is decreased in obese subjects fulfilling three or more criteria of MetS, suggesting a state of relative leptin deficiency in obesity associated with advanced stages of MetS. Arq Bras Endocrinol Metab. 2009;53(9):1088-95

Keywords
Leptin; adipokines; obesity; metabolic syndrome; leptinemia

RESUMO

Objetivo: Avaliar as associações entre leptinemia e os componentes da síndrome metabólica (MetS).

Métodos: Cinquenta e um adultos obesos (9 homens, 36,7 ± 10,0 anos, índice de massa corpórea, IMC, 46,2 ± 10,0 kg/m²) foram submetidos à avaliação clínica, a determinações da massa adiposa (BF; bioimpedância) e do gasto energético basal (REE, calorimetria indireta) e a análises hormonais e bioquímicas. Os pacientes foram divididos em três grupos, de acordo com o número de critérios para MetS: Grupo I, nenhum ou 1; Grupo II: 2; e Grupo III: 3 ou 4 critérios.

Resultados: A leptinemia absoluta (LepA; 37,5 ± 16,9 ng/mL) se correlacionou diretamente com IMC (r = 0,48; p = 0,0004), circunferência abdominal (r = 0,31; p = 0,028) e BF (r = 0,52; p = 0,0001). Leptinemia ajustada por BF (LepBF) se correlacionou inversamente ao peso (r = -0,41; p = 0,027), ao REE (r = -0,34; p = 0,01) e ao número de critérios para MetS (r = -0,32; p = 0,02). Não houve diferença de LepA entre os grupos. LepBF no Grupo III (0,58 ± 0,27 ng/mL/kg) foi significativamente menor que no Grupo I (0,81 ± 0,22 ng/mL/kg; p = 0,03) e II (0,79 ± 0,30 ng/mL/kg; p = 0,02).

Conclusões: A produção de leptina pelo tecido adiposo está diminuída em pacientes obesos que preenchem três ou mais critérios para MetS, sugerindo um estado de deficiência relativa de leptina na obesidade associada a estágios avançados de MetS. Arq Bras Endocrinol Metab. 2009;53(9):1088-95

Descritores
Leptina; adipocinas; obesidade; síndrome metabólica; leptinemia
INTRODUCTION

Obesity is a chronic disease that has reached epidemic proportions worldwide. According to the World Health Organization (WHO), over a billion adults are overweight, and at least 300 million are obese – defined as body mass index (BMI) over 30 kg/m² (1). Among Brazilians above age 20, 40.6% are overweight and 11% are obese (2).

The increasing prevalence of obesity leads to the development of common metabolic disturbances, such as atherogenic dyslipidemia, elevated arterial blood pressure, insulin resistance or hyperglycemia, inflammation and prothrombotic states. The association of these disturbances with visceral obesity is defined as metabolic syndrome (MetS) (3).

Leptin, the product of the OB gene, plays an important role in this homeostatic system. Among other actions, leptin regulates food intake stimulating hypothalamic anorexigenic pathways and inhibiting orexigenic ones (4,5). In addition, leptin has been associated with MetS in completely leptin-deficient animals and humans (6-11), as well as in partially-deficient models (12).

In the periphery, leptin attenuates the lipogenic and oxidative actions of insulin, increases β-oxidation of nonesterified fatty acid (NEFA) and decreases its esterification into triacylglycerol (13). Taken together, peripheral actions of leptin decrease lipogenesis and protect against tissue lipotoxicity (14,15). Thus, decreased leptin production by adipose tissue might potentially contribute to the development of MetS.

Leptin has been implicated in inflammation, thrombogenesis and fibrinolysis (16-18), but it is yet unclear whether leptin is merely a biomarker of MetS and cardiovascular disease (16,19), or whether it is directly involved in the pathogenesis of those conditions (16,20-24).

In this study, we aimed to evaluate whether leptinemia is associated with the components of MetS and its severity. To achieve that objective, we evaluated both absolute leptin levels (LepA) and leptin levels adjusted for body fat (LepBF) in obese subjects who fulfilled 0-1, 2 or 3-4 of the International Diabetes Federation (IDF) criteria for MetS (25), and correlated the values with their anthropometric, metabolic and hormonal parameters.

PATIENTS AND METHODS

Patients

This was a cross-sectional study of a consecutive cohort of adult obese patients followed-up in the Obesity Outpatient Clinic of the Hospital de Clínicas of Universidade Federal do Paraná (UFPR), Curitiba, Brazil. From June to December 2006, a total of 225 medical records from patients with BMI > 30 kg/m² was reviewed for the selection of patients eligible for the study. Only adult obese patients whose weight had been stable in the previous three months and who agreed to participate were included. We excluded pregnant women, patients with severe comorbidities or chronic diseases, with evidence of secondary obesity due to genetic, endocrine, metabolic or neurologic disorders, and patients who received during the past 12 months corticosteroids, antidiabetic therapy, antiobesity drugs or any other pharmacologic agent known to influence body weight or serum leptin levels.

Methods

Clinical examination and anthropometric measurements were performed by the same investigator in the morning, while subjects were fasting for 12 hours. Starting from the day before measurements, patients were advised not to take any drugs, not to engage into physical activity and to drink at least 2 L of water over 24 hours.

Arterial blood pressure was measured twice, while patients were sitting, with a 10-minute interval. The average of the two measurements was used for the analysis. Patients were weighed while wearing light street clothes on a digital scale with 0.01-kg increments (PL-180 LED, Filizola Balanças Industriais, São Paulo, SP, Brazil). Heights were measured using a stadiometer attached to the same scale, with 0.5-cm increments. Waist circumference (WC) was measured with a flexible measuring tape with 0.1-cm increments, by placing the tape on the widest abdominal perimeter between the last rib and the iliac crest, parallel to the floor, while standing.

Body fat mass (BF, in kg) was measured by bioelectric impedanceometry (BIA 310 bioimpedance analyzer, Biodynamics Corporation, Seattle, WA, USA). The Lohman equation for obese individuals was used to determine BF. Resting energy expenditure (REE) was assessed by indirect calorimetry (Deltatrac II, SensorMedics, Anaheim, CA, USA). Briefly, REE was estimated from oxygen consumption (VO₂) and carbon dioxide production (VCO₂) measured during 30 minutes, and extrapolated to 24 hours.

A 12-hour fasting morning blood sample was collected once from each subject for measurements of glucose, insulin, total cholesterol (TC), triglyceride (TGC), and high-density lipoprotein (HDL) cholesterol by routine methods at our laboratory. Low-density lipo-
protein (LDL) cholesterol values were obtained from Friedewald equation: LDL = TC - (HDL+TGC/5). Aliquots of blood sample were used for determination of TSH (chemiluminescence, DPC, Los Angeles, CA, normal range 0.4-4.0 μUI/mL, limit of detection 0.03 μUI/mL, CV 3.8-12.5%), free T4 (chemiluminescence, DPC, Los Angeles, CA, normal range 0.8-1.8 ng/dL, CV 4.4-9.0%), insulin (chemiluminescence, DPC, Los Angeles, CA, normal range 6-27 μUI/mL, limit of detection 0.5 ng/mL, CV 3.4-8.3%). Samples for leptin were assayed in duplicate, and the mean CV was 5.55 ± 4.68%. Leptin levels were expressed as absolute leptinemia (ng/mL; LepA) and as leptinemia adjusted for BF (ng/mL/kg; LepBF). The homeostatic model assessment of insulin resistance index (HOMA-IR) was calculated according to the equation: fasting glucose (mmol/L) x fasting insulin (μU/mL) / 22.5.

Based on the clinical, anthropometric and laboratory data, we categorized the patients into three groups, using the IDF criteria for diagnosis of MetS (25). Those criteria require the presence of central obesity (defined as increased WC, adjusted for gender and different ethnic groups) associated with two or more of the following criteria:

1. elevated triglycerides (≥ 150 mg/dL) or specific treatment for hypertriglyceridemia;
2. reduced HDL cholesterol (< 50 mg/dL in females and < 40 mg/dL in males) or specific treatment for this lipid abnormality;
3. elevated blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg) or treatment for previously diagnosed hypertension;
4. elevated fasting plasma glucose (≥ 100 mg/dL) or previously diagnosed type 2 diabetes mellitus (T2DM) (25).

Patients were categorized into one of the three groups: Group I (patients with central obesity who fulfill 0 or 1 criterion for MetS), Group II (patients with central obesity who fulfill 2 criteria for MetS) and Group III (patients with central obesity who fulfill 3 or 4 criteria for MetS). Since all patients had BMI > 30 kg/m² all of them were assumed to have central obesity according to the IDF recommendations.

The study was approved by the Ethics Committee for Research in Human Beings of Hospital de Clínicas of UFPR, and a written Informed Consent was given by all subjects.

Statistical analysis was performed using the Statgraphics Plus for Windows 3.0 (Manugistics, Inc., Rockville, MD, USA) and STATISTICA 7.0 (Statsoft, Inc, Tulsa, OK, USA). Data were reported as means ± standard deviation (SD), and p < 0.05 was considered to be significant. Measures of central tendency and variability were calculated for continuous variables. Synthetic tables of frequency were elaborated for qualitative variables. Distribution was determined by the Kolmogorov-Smirnov and Lilliefors tests. Parametric tests (ANOVA) were used when distribution was normal, whereas the Kruskal-Wallis test was used when distribution was asymmetric. Pearson’s or Spearman’s correlation coefficients were used to determine the correlation between variables, according to the type of distribution.

RESULTS

The study group consisted of 51 obese participants. Six patients had obesity class I (BMI = 30-34.9 kg/m²), 11 had obesity class II (BMI = 35-39.9 kg/m²) and 34 had obesity class III (BMI > 40 kg/m²). Table 1 shows the main characteristics of all patients and of the subgroups according to the number of risk factors for MetS.

Weight, BMI, WC and BF were significantly higher in patients of Group III in comparison with patients of Group I (all p < 0.001). In addition, Group III had higher systolic (SBP, 131.8 ± 9.5 mmHg versus 120.6 ± 11.9 mmHg; p < 0.05) and diastolic blood pressure (DBP, 84.1 ± 7.1 mmHg versus 77.7 ± 4.4; p < 0.05) in comparison with Group I. Patients of Group I had REE of 1,560.0 ± 201.9 kcal/day – a value significantly lower than those observed in Group II (1,975.7 ± 325.6 kcal/day; p < 0.05) and III (2,267.1 ± 487.7 kcal/day; p < 0.001).

Patients in Group I had lower levels of fasting glucose (p < 0.05), triglycerides (p < 0.001), insulin (p < 0.05) and HOMA-IR (p < 0.001) in comparison with the other two groups. Fasting glucose (p < 0.05) and triglycerides levels (p < 0.001) were also lower in Group II compared to Group III. Table 2 summarizes the biochemical and hormonal findings.

Among all patients absolute serum leptin levels (LepA) were 37.5 ± 16.9 ng/mL (range 8.3-81.9 ng/mL), BF was 52.8 ± 16.5 kg (range 25.4-88.2 kg) and LepBF was 0.73 ± 0.29 ng/mL/kg (range 0.19-1.35 ng/mL/kg). LepA was positively correlated with weight (r = 0.37; p = 0.008), BMI (r = 0.48; p < 0.001), WC (r = 0.31; p < 0.05) and BF (r = 0.52; p < 0.001), whereas LepBF was inversely correlated with weight (r = -0.31;
p < 0.05) and REE (r = -0.34; p = 0.01). The number of risk factors for MetS did not correlate with LepA (r = -0.02; p = 0.9), but it showed a significant negative correlation with LepBF (r = -0.32; p = 0.02) (Figure 1).

LepA did not differ among the groups (Group I: 33.59 ± 14.79 ng/mL; Group II: 42.42 ± 17.59 ng/mL; Group III: 34.48 ± 17.01 ng/mL), regardless of significant differences in weight, BMI, WC and BF (Table 3). However, LepBF was 0.58 ± 0.27 ng/mL/kg in patients of Group III, a value significantly lower than those observed in patients of Group I (0.81 ± 0.22 ng/mL/kg, p = 0.03) and Group II (0.79 ± 0.30 ng/mL/kg, p = 0.02) (Figure 2). There was no clear cut-off value for LepA or LepBF that could distinguish obese patients according to the number of risk factors for MetS.

We have performed analysis of the LepA and LepBF for each risk factor associated with MetS separately (Table 3). In patients with hypertriglyceridemia (triglycerides levels ≥ 150 mg/dL, n = 26), LepBF was significantly higher than in those 25 patients with normal triglycerides levels (0.83 ± 0.26 ng/mL/kg versus 0.63 ± 0.28 ng/mL/kg; p = 0.01). As shown in Table 3, LepBF tended to be lower in patients with abnormal blood pressure (0.70 ± 0.31 ng/mL/kg versus 0.78 ± 0.23 ng/mL/kg), hyperglycemia (0.68 ± 0.32 ng/mL/kg versus 0.79 ± 0.24 ng/mL/kg) and low HDL-cholesterol (0.69 ± 0.26 ng/mL/kg versus 0.77 ± 0.32 ng/mL/kg), but none of these values reached statistical significance. In contrast, LepA did not differ in the presence or absence of the risk factors.

**Table 1.** Characteristics of the whole cohort of patients and in each study group divided according to the number of risk factors for metabolic syndrome: Group I (0 or 1), Group II (2), and Group III (3 or 4)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 51)</th>
<th>Group I (n = 13)</th>
<th>Group II (n = 21)</th>
<th>Group III (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.7 ± 10.0</td>
<td>37.7 ± 8.6</td>
<td>35.8 ± 12.1</td>
<td>36.9 ± 8.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>119.0 ± 28.1</td>
<td>97.0 ± 22.1</td>
<td>119.1 ± 21.8</td>
<td>135.2 ± 29.0a</td>
</tr>
<tr>
<td>Sex (females:males)</td>
<td>46.5</td>
<td>12.1</td>
<td>19.2</td>
<td>11.6</td>
</tr>
<tr>
<td>Race (Caucasians:Afro-Brazilians)</td>
<td>46.5</td>
<td>13.0</td>
<td>19.2</td>
<td>14.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>119 ± 28.1</td>
<td>97.0 ± 22.1</td>
<td>119.1 ± 21.8</td>
<td>135.2 ± 29.0b</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>46.2 ± 10.0</td>
<td>39.3 ± 8.6</td>
<td>46.8 ± 10.2</td>
<td>50.6 ± 8.2b</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>125.1 ± 18.5</td>
<td>114.9 ± 19.1</td>
<td>124.0 ± 16.7</td>
<td>134.3 ± 16.4a</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>127.0 ± 12.2</td>
<td>120.6 ± 11.9</td>
<td>127.1 ± 13.1</td>
<td>131.8 ± 9.5c</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>82.4 ± 6.5</td>
<td>77.7 ± 4.4</td>
<td>83.8 ± 5.9</td>
<td>84.1 ± 7.1d</td>
</tr>
<tr>
<td>BF (kg)</td>
<td>52.8 ± 16.5</td>
<td>41.3 ± 16.1</td>
<td>53.9 ± 14.6</td>
<td>60.2 ± 14.9c</td>
</tr>
<tr>
<td>REE (kcal/d)</td>
<td>1,967.1 ± 449.3</td>
<td>1,560.0 ± 201.9a</td>
<td>1,975.7 ± 325.6</td>
<td>2,267.1 ± 487.7</td>
</tr>
</tbody>
</table>

BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; BF: body fat; REE: resting energy expenditure.

* p < 0.001 versus Group I; † p < 0.05 versus Group I; ‡ p < 0.01 versus Group I; § p < 0.05 versus Group II and p < 0.001 versus Group III.

**Table 2.** Biochemical and hormonal parameters of the whole cohort of patients and in each study group divided according to number of risk factors for metabolic syndrome: Group I (0 or 1), Group II (2), and Group III (3 or 4)

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 51)</th>
<th>Group I (n = 13)</th>
<th>Group II (n = 21)</th>
<th>Group III (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>107.4 ± 24.5</td>
<td>88.7 ± 5.2†</td>
<td>105.2 ± 19.6d</td>
<td>124.3 ± 27.8</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>193.3 ± 34.5</td>
<td>181.5 ± 30.2</td>
<td>191.3 ± 38.3</td>
<td>204.7 ± 30.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>161.8 ± 90.4</td>
<td>100.4 ± 34.9†</td>
<td>152.0 ± 111.1†</td>
<td>220.8 ± 48.2</td>
</tr>
<tr>
<td>HDL-c (mg/dL)</td>
<td>48.0 ± 12.0</td>
<td>54.3 ± 10.1</td>
<td>50.1 ± 13.0</td>
<td>40.6 ± 8.4</td>
</tr>
<tr>
<td>LDL-c (mg/dL)</td>
<td>113.7 ± 27.7</td>
<td>104.1 ± 23.1</td>
<td>115.1 ± 29.8</td>
<td>119.2 ± 28.0</td>
</tr>
<tr>
<td>TSH (uUI/mL)</td>
<td>2.41 ± 1.56</td>
<td>2.18 ± 1.53</td>
<td>2.38 ± 1.60</td>
<td>2.61 ± 1.59</td>
</tr>
<tr>
<td>Free T4 (ng/dL)</td>
<td>1.21 ± 0.23</td>
<td>1.23 ± 0.21</td>
<td>1.19 ± 0.22</td>
<td>1.23 ± 0.26</td>
</tr>
<tr>
<td>Insulin (uUI/mL)</td>
<td>22.95 ± 12.59</td>
<td>13.06 ± 5.62†</td>
<td>21.99 ± 8.43</td>
<td>31.70 ± 14.85</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>6.55 ± 5.38</td>
<td>2.85 ± 1.20†</td>
<td>5.75 ± 2.48</td>
<td>10.36 ± 7.37</td>
</tr>
</tbody>
</table>

TC: total cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance index.

* p < 0.05 versus Group II and Group III; † p < 0.05 versus Group I; ‡ p < 0.01 versus Group I; § p < 0.05 versus Group II and p < 0.001 versus Group III.
Table 3. Absolute serum levels of leptin (LepA) and leptinemia adjusted for BF (LepBF) according to the presence or absence of risk factors for metabolic syndrome

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Fasting glucose</th>
<th>Triglycerides</th>
<th>HDL-c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n = 15)</td>
<td>High (n = 36)</td>
<td>Normal (n = 24)</td>
</tr>
<tr>
<td>LepA (ng/mL)</td>
<td>40.2 (16.3)</td>
<td>36.4 (17.3)</td>
<td>35.3 (13.5)</td>
</tr>
<tr>
<td>LepBF (ng/mL/kg)</td>
<td>0.78 (0.23)</td>
<td>0.70 (0.31)</td>
<td>0.79 (0.24)</td>
</tr>
</tbody>
</table>

Data shown as mean (SD).
* p = 0.01 versus normal triglycerides.

**DISCUSSION**

In our cohort of obese individuals, although LepA was positively correlated with weight, BMI, WC and BF as expected, no associations were found between LepA and any component of MetS. In addition, LepA was not associated with severity of MetS since its levels were similar among patients with different degrees of MetS. However, we did observe that leptin levels adjusted for body fat mass (LepBF) were significantly decreased in obese patients with at least three risk factors for MetS. The fact that LepBF was negatively correlated with the number of risk factors provides further evidence that LepBF may be associated with the severity of MetS.

There have been reports showing positive correlation between leptinemia and risk factors associated with MetS, such as hypertension (26,27), DM (28), hypertriglyceridemia and low HDL-cholesterol (29). However, several studies have been unable to replicate these findings (30-37). It is likely that the contradictions among the studies arise from the fact that leptinemia is not adjusted for the amount of BF in most studies. By adjusting leptinemia we could, for the first time, identify correlations between leptin and MetS. In agreement with our results, another study has clearly demonstrated that high leptin levels have protective actions against the development of diabetes in obesity (38).
In this study, we showed that obese patients with three or more criteria for MetS have lower levels of leptin adjusted to fat body mass (LepBF), when compared to their obese counterparts with less than three criteria. This observation was not true when LepA was considered. Moreover, we could not establish cut-off values of leptinemia in order to predict the number of criteria fulfilled for MetS. Several studies showed positive correlations between leptinemia and the criteria for MetS, such as hypertension, DM, hypertriglyceridemia and low HDL-c. However, other studies did not replicate those findings. It is possible that these contradictions are attributed to the fact that some of these studies did not adjust leptinemia to the parameters of obesity (weight, BMI and BF) (39). However, when leptinemia is adjusted to those parameters, high leptin levels may have protective action against the development of diabetes in obese patients, in concordance to our findings.

Although the correlation between leptinemia and body weight is unquestionable, we (40) and other investigators (34,41-43) have documented high variability of leptin levels among patients with similar BMI and BF, particularly in obesity. As a consequence, not all studies with extremely high levels of leptin, as it would be expected. This is true even in the monogenic syndrome of obesity caused by mutations in the leptin receptor, where circulating levels of leptin are highly variable among affected individuals and not disproportionately elevated (44). In our series, 34 out of 51 subjects had severe obesity with BMI above 40 kg/m². Within this subgroup, leptin levels varied 7-fold (from 11.6 ng/mL to 81.9 ng/mL; data not shown). Although common obesity is mostly related to leptin-resistance, a subgroup of subjects with severe obesity and inappropriately low circulating levels of leptin was identified in our study by using LepBF instead of LepA in the analysis. In this subgroup of patients, disproportionately low production of leptin by the adipose tissue, and not leptin-resistance, is the possible mechanism to explain their excessive body weight and metabolic abnormalities. In agreement with that observation, mice partially deficient in leptin under high-fat feeding show an increased risk of obesity, hepatic steatosis, glucose intolerance, and hyperlipidemia (45). Moreover, humans heterozygous for mutations of the OB gene with partial leptin deficiency have an increased prevalence of overweight and obesity (12).

In our study, LepBF was inversely correlated with weight and REE. These findings support the evidence that more obese patients – and, therefore, with higher REE, have disproportionately lower leptin levels adjusted for their fat mass. Moreover, the analysis of individual components of the MetS showed a significant association of low LepBF and hypertriglyceridemia. This finding might be explained by the antilipogenic and pro-lipolytic effects of leptin on the metabolism of fatty acids (33,35,46,47). In addition, we observed that LepBF tended to be lower in patients with abnormal blood pressure, hyperglycemia and low HDL-cholesterol, although the values did not reach significance.

Peripheral effects of leptin decreases lipogenesis and protects against excessive weight gain, both acutely and chronically. Accordingly, reduced peripheral actions of leptin would lead to increased lipogenesis and accumulation of lipids in sites other than the adipose tissue – a phenomenon known as lipotoxicity (14,15). There is strong evidence that lipotoxicity takes part in the development of several components of the MetS, such as hepatic steatosis, insulin resistance, dyslipidemia, beta cell failure and T2DM (48,49). When comparing equal masses of visceral and subcutaneous adipose tissue, both secrete similar amounts of lipids to the bloodstream, whereas visceral fat secretes less leptin. In our patients who presented with three or four risk factors for MetS, low leptin levels might reflect the lack of balance between lipid and leptin secretion by visceral and subcutaneous adipose tissue (50). Consequently, less leptin might be available to the peripheral tissues, which may predispose to lipotoxicity and the development of comorbidities associated with MetS in these individuals. However, there was no clear cut-off value of LepBF to identify obese patients with high risk for MetS.

Our study has some limitations. Its cross-sectional design does not allow us to definitively answer whether the lower levels of LepBF observed in our patients is truly involved in the pathogenesis of the MetS, or if it is just a biomarker of the disease. Nevertheless, this situation resembles what is observed in T2DM, in which both abnormal insulin secretion and insulin resistance play a role in the development of the disease (51). In addition, we could not identify any significant correlations between LepBF and additional variables, other than triglycerides. This was probably due to the size of our cohort, which was influenced by the very strict criteria for enrollment in our study, especially the exclusion of severe comorbidities and several medications usually taken by obese subjects with BMI greater than 40 kg/m². On the other hand, we were able to have a
more homogeneous study group for the analysis, avoiding various confounding factors that might influence body weight, LepA and LepBF.

In conclusion, we have found that obese patients with three or more risk factors for MetS, especially those with hypertriglyceridemia, have lower levels of LepBF when compared to their obese counterparts with less than three risk factors and normal triglycerides. Considering that our patients with three or more risk factors were heavier and had more elevated triglycerides in comparison with the other groups, and that LepA did not differ among the study groups, our LepBF findings suggest a state of relative leptin deficiency in obesity associated with more advanced stages of MetS. If this hypothesis proves to be true in future studies therapy with leptin or some agonists will be useful in selected obese patients to prevent or to ameliorate some components of MetS, as already reported in various forms of relative leptin deficiency, such as anorexia nervosa, milder forms of hypothalamic amenorrhea, and congenital or acquired lipodystrophy (52).

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES


