Leptin, leptin receptors, nerve growth factor and TrkA in women with metabolic syndrome

ABSTRACT
Adipose tissue is now recognized to be an important endocrine organ, secreting a variety of adipokines that are involved in the regulation of energy metabolism, insulin resistance and metabolic syndrome. Metabolic syndrome (MetSyn) corresponds to a sub-clinical inflammatory condition in which white adipose tissue (WAT) is characterized by an increased production and secretion of inflammatory molecules which may have local effects on WAT physiology but also systemic effects on other organs. Our purpose is to study the expression of some adipokines (leptin, Ob-R, NGF and TrkA) in women with metabolic syndrome. Our results reveal that women with MetSyn have significantly higher BMI, WC, insulinemia, total cholesterol and low high-density lipoprotein-cholesterol levels. Plasma levels of leptin and NGF are over-expressed. The immunohistochemical expression of leptin, leptin receptors, NGF and TrkA are very strong thus corresponding immunochemical data. The locally-produced pro-inflammatory adipokines leptin and NGF and their receptors are overproduced in MetSyn. They probably contribute to the ethiopathogenic mechanism underlying the metabolic derangements and cardiovascular disorders in MetSyn implicating in the obese state, insulin resistance and hypertension.

Key words: metabolic syndrome, prehypertention, adipokines

Introduction
It is now well established that obesity is an independent risk factor for type 2 diabetes, dyslipidemia, and cardiovascular diseases. A recent and striking discovery is that obesity is associated with a low-grade inflammation process in adipose tissue, the pathophysiological mechanisms of which remained poorly understood, underlining the relationship between fat cells and the immune system. Another physiological and pathological aspect that has generated a considerable sum of experimental and clinical work during the last decade is that adipocytes have the capacity to synthesize and secrete several factors collectively called adipokines. Some of them appear to play an important role in obesity-associated insulin resistance and cardiovascular complications (Das, 2002a, 2002b). Chronic, low-grade inflammation may be a common soil involving the pathogenesis of metabolic syndrome (MetS) and cardiovascular disease (Yang et al., 2012). Several studies have shown that adipokine production is altered in obesity, type 2 diabetes and metabolic syndrome (Samad et al., 1996, 1997; Fried et al., 1998; Bastard et al., 2002; Sartipy & Loskutoff, 2003). Some adipokines are increased in the obese state and have been implicated in insulin resistance (TNF-alpha, IL-6, resistin). Conversely, leptin and adiponectin both exert an insulin-sensitizing effect. In obesity, insulin resistance has been linked to leptin resistance (Guerre-Millo, 2004). The obese gene product, leptin, plays a central role in food intake and energy metabolism. Leptin, a hormone linking adiposity and central nervous circuits to reduce appetite and enhance energy expenditure, has been shown to
increase overall sympathetic nerve activity, facilitate glucose utilization and improve insulin sensitivity (Ren, 2004).

Our purpose is to study the expression of some adipokines (leptin, Ob-R, NGF and TrkA) in women with metabolic syndrome.

Materials and Methods

Sixty adult women with MetSyn were included in the study. The MetSy was defined by an unified criteria set by several major organizations. The waist circumference (WC), body mass index (BMI), glucose, insulin and lipids were measured for each subject. The total body fat composition was measured in every participant with a commercially available bio-impedance meter. Plasma leptin and NGF levels were measured by ELISA. Leptin, Ob-R, NGF and TrkA immunohistochemical expression was analyzed by the ABC method in WAT s.c. adipose tissue of a subgroup of 10 women using primary polyclonal rabbit antibody for leptin (Santa Cruz Biotechnology, USA).

Results

Our results reveal that women with MetSyn have significantly higher BMI, WC, insulinemia, total cholesterol and low high-density lipoprotein-cholesterol levels (Table 1).

Table 1. Some clinical chemical indexes.

<table>
<thead>
<tr>
<th>INDEXES</th>
<th>GROUPS</th>
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<tbody>
<tr>
<td>Total CHOL</td>
<td>Controls</td>
<td>MetSyn</td>
<td></td>
</tr>
<tr>
<td>mmol.L⁻¹</td>
<td>4.1±0.9</td>
<td>6.3±0.28</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>TRIGLY</td>
<td>1.5±0.3</td>
<td>2.1±0.73</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>mmol.L⁻¹</td>
<td>4.46±1.53</td>
<td>6.91±1.04</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

All the subjects with MetSyn showed significantly higher plasma levels of NGF. Plasma levels of leptin are elevated. The immunohistochemical expression of leptin and leptin receptors (Ob-R) are over-expressed. (Figures 1 and 2) NGF and TrkA immunohistochemical reactions are also very strong. (Figures 3 and 4). Thus they are corresponding immunochemical data. The waist circumference, body mass index (BMI), and body composition variables (visceral fat level, total body fat, and total body muscle mass) are correlates of the leptin and NGF expression.

Discussion

Our study demonstrates that leptin and its receptors as well as NGF TrkA and over-expressed in subjects with MetSy. These findings correlate with the results of other authors reporting NGF is upregulated in obesity, type 2 diabetes, and the MetSyn (Bullo et al., 2007).
Like them we found that plasma NGF was correlated with body mass index (BMI), percentage body fat, and waist circumference. More over our study demonstrated that leptin levels were also positively related to lipid profile, waist circumference, BMI and body composition variables. We accept that alteration of WAT mass in obesity as a part of MetSy affects the production of most adipose secreted factors. Since both conditions are associated with multiple metabolic disorders and increased risk of cardiovascular diseases, the idea has emerged that WAT could be instrumental in these complications, by virtue of its secreted factors. Circulating levels and adipose tissue mRNA expression of leptin are strongly associated with BMI and fat mass in obesity (Considine et al., 1996; Vidal et al., 1996). Thus, leptin appears as a real marker of adipose tissue mass in humans where the subcutaneous fraction represents about 80% of total fat. Evidence has suggested that leptin plays a specific role in the intricate cascade of cardiovascular events, in addition to its well-established metabolic effects. These findings have prompted the speculation that leptin in the physiological range may serve as a physiological regulator of cardiovascular function whereas elevated plasma leptin levels may act as a pathophysiological trigger and/or marker for cardiovascular diseases due to tissue leptin resistance.

Conclusion

The locally-produced pro-inflammatory adipokines leptin and NGF and their receptors are overproduced in MetSyn. They probably contribute to the ethiopathogenic mechanisms underlying the metabolic derangements and cardiovascular disorders in MetSyn implicating in the obese state, insulin resistance and hypertension.

References


RESEARCH ARTICLE