Insulin resistance and metabolic syndrome in outpatients with bipolar disorder

Resistência à insulina e síndrome metabólica em pacientes ambulatoriais com transtorno do humor bipolar

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Abstract

Background: Bipolar disorder (BD) is associated with significant morbidity and mortality from metabolic diseases. There is a paucity of data regarding insulin resistance (IR) and its relationship with the metabolic syndrome (MS) in bipolar patients. Objective: To evaluate the prevalence of both IR and MS in BD outpatients and to assess clinical criteria associated with IR. Method: Cross-sectional study in 65 DSM-IV-TR BD patients consecutively assessed at the Bipolar Disorder Program at Hospital de Clinicas de Porto Alegre, Brazil. IR was diagnosed by the homeostatic model assessment – insulin resistance (HOMA-IR) and MS was diagnosed using three different definitions: National Cholesterol Educational Program – Adult Treatment Panel III (NCEP-ATP III); NCEP-ATP III modified criteria and International Diabetes Federation. Results: IR was present in 43.1% of the sample (women 40%, men 44.4%). The prevalence of MS defined by the NCEP-ATP III criteria was 32.3%, NCEP-ATP III modified was 40% and IDF was 41.5%. NCEP-ATP III modified criteria showed the best trade-off between sensitivity (78.6%) and specificity (89.2%) to detect insulin resistance. Waist circumference was the clinical parameter most associated with IR. Discussion: Current MS criteria may provide reasonable sensitivity and specificity for the detection of IR in BD patients. Abdominal obesity is closely related to IR in this patient population.


Keywords: Insulin resistance, metabolic syndrome X, abdominal fat, bipolar disorder.

Resumo

Contexto: O transtorno bipolar (TB) está associado a uma significativa morbi-mortalidade por causas metabólicas. Existem poucos dados sobre a prevalência de resistência à insulina (RI) e sua relação com a síndrome metabólica (SM) em pacientes com TB. Objetivo: Avaliar a prevalência de RI e SM em pacientes bipolares ambulatoriais e identificar os parâmetros clínicos associados à RI. Método: Estudo transversal em 65 pacientes com TB diagnosticados pelos critérios do DSM-IV-TR, avaliados de forma consecutiva no Programa de Transtorno Bipolar do Hospital de Clinicas de Porto Alegre, Brazil. RI foi diagnosticada utilizando o homeostatic model assessment – insulin resistance (HOMA-IR) e a SM foi diagnosticada utilizando três definições diferentes: do National Cholesterol Educational Program – Adult Treatment Panel III (NCEP-ATP III); NCEP-ATP III modificado e da International Diabetes Federation. Resultados: A prevalência de RI foi 43,1% (mulheres 40%, homens 44,4%). A prevalência de SM definida pelo NCEP-ATP III foi 32,3%, pelo NCEP-ATP III modificado foi 40% e pela IDF foi 41,5%. Os critérios do NCEP-ATP III modificado demonstrou a melhor relação entre sensibilidade (78,6%) e especificidade (89,2%) na detecção de RI. Conclusão: As definições atuais de SM podem identificar, com razoável sensibilidade e especificidade, RI em pacientes com TB. A obesidade abdominal é bastante associada à RI nessa população de pacientes.


Palavras-chave: Resistência às insulina, síndrome X metabólica, gordura abdominal, transtorno bipolar.

Introduction

The insulin resistance syndrome was first proposed by Reaven1 under the term syndrome X in order to emphasize the importance of insulin resistance (IR) and compensatory hyperinsulinemia in cardiovascular morbidity. IR have been associated not only to the development of type 2 diabetes, dyslipidemia, arterial hypertension, cardiovascular disease and cancer2 but also to impairment of functioning and cognitive decline1. The metabolic syndrome (MS) is a clinical concept that emerged as a proxy for IR in order to diagnose individuals at increased risk for cardiovascular disease who needed appropriate care.

Currently, there is a lot of controversy about the correspondence of the MS to IR and it may be related to the definition of its component, since they are designed to be sensitive and clinically useful but do not necessarily reflect subjacent insulin resistance. Current criteria for MS include measures of abdominal obesity, elevated blood pressure, triglycerides and fasting blood glucose as well as decreased HDL-cholesterol levels4-6. Increased intra-abdominal fat, as measured by waist circumference, have been consistently regarded as an important contributor to IR in several studies4-6

Bipolar disorder (BD) is associated with increased morbidity and mortality due to general medical conditions such as cardiovascular disease, obesity and diabetes5,11. Some recent studies have addressed the prevalence of the MS in BD patients from different countries, reporting alarming rates ranging from 16.7% to 49%12-15. Nonetheless, only a few recent studies have specifically addressed the issue of IR in BD using validated methods. Hung et al.16 studied a small sample of...
non-obese young males and found an inverse relationship between the severity of unipolar and bipolar depressive symptoms and insulin resistance. In the same vein, Stemmel et al.\textsuperscript{17} found high rates of hyperlipidemia and IR in untreated women with bipolar II disorder. Although preliminary, these data have added some insights into the underlying pathophysiology of previous findings of increased IR and metabolic disturbances in patients with bipolar disorder\textsuperscript{18,19}.

We performed a cross-sectional study in a sample of outpatients with rigorously defined BD to assess the prevalence of IR and MS and to explore the correspondence of individual MS criteria, as defined by different consensus statements, with IR in order to determine its clinical correlates in this population.

**Methods**

**Subjects**

The study was a cross-sectional analysis of 65 outpatients with BD, 18 years or older, consecutively recruited from January to August 2007 from the Bipolar Disorders Program of the Hospital de Clínicas, Porto Alegre, Brazil. The study was approved by the Hospital Institutional Review Board (GPPG 06-245) and patients gave written informed consent before entering the study. All patients met DSM-IV-TR criteria for BD, diagnosed with the SCID-I\textsuperscript{20} confirmed by two senior psychiatrists.

Clinical and laboratory data

Clinical, demographic, anthropometrical and metabolic measures were assessed at the first visit. These included height and weight, body mass index (BMI), waist circumference and blood pressure. Patients were requested to have a fasting blood sample drawn the next day to evaluate fasting serum glucose, insulin, total and high density cholesterol (HDL) and triglycerides levels. Patients had a second study visit to receive test results and counseling. Medical referral was provided for those who needed treatment.

**Determination of insulin resistance and metabolic syndrome diagnosis**

IR was evaluated with the homeostatic model assessment – insulin resistance (HOMA-IR)\textsuperscript{21}. The HOMA-IR was calculated as \[\frac{\text{fasting glucose (mmol/L) x fasting insulinemia (mU/L)}}{22.5}\]. Following recent published data for the Brazilian population, we classified patients with a HOMA-IR score > 2.71 as insulin resistant\textsuperscript{22}. Three definitions were applied to categorize subjects as meeting criteria for the MS: National Cholesterol Educational Program – Treatment Adult Panel III (NCEP-ATP III)\textsuperscript{6}, NCEP-ATP III modified criteria\textsuperscript{5} and International Diabetes Federation (IDF)\textsuperscript{7}.

**Statistical analysis**

Sensitivity and specificity were calculated for individual criteria as well as for definitions of MS in relation to dichotomized IR. Standard ROC curves were generated for comparison of areas under the curve. The HOMA-IR index was log-transformed for the multiple linear regression analysis, and the components of MS were tested as predictors using backward selection of variables. All tests were two-tailed.

**Results**

Sixty-five patients were included in the study. Of these, 69.2% were female (mean age 46 ± 12.5 years) and 30.8% male (mean age 44.6 ± 12.4 years). Most patients were on multiple medications (median 2 IQR 2 – 3). Median values for HOMA-IR were 2.27 (IQR 1.48 – 4.39) and for insulin 9.25 (IQR 6.98 – 15.52). The prevalence of IR was 43.1% (women 40%, men 44.4%). Demographic and clinical data are shown in table 1. The prevalence of the MS defined by the NCEP-ATP III definition was 32.3% (women 24.4%, men 50%), NCEP-ATP III modified was 40% (women 35.6%, men 50%) and IDF was 41.5% (women 35.6%, men 55%). Performance of individual MS criteria and criteria sets is displayed in table 2.

**Table 1. Demographic and clinical data of BD patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 65)</th>
<th>Insulin-resistant (n = 28)</th>
<th>Non insulin-resistant (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean ± SD*</td>
<td>45.6 ± 12.4</td>
<td>49.1 ± 12.9</td>
<td>42.9 ± 11.5</td>
</tr>
<tr>
<td>Female sex: n (%)</td>
<td>45 (69.2)</td>
<td>20 (71.4)</td>
<td>25 (67.6)</td>
</tr>
<tr>
<td>Years of education: mean ± SD</td>
<td>9.2 ± 4.2</td>
<td>8.5 ± 4.6</td>
<td>9.6 ± 3.9</td>
</tr>
<tr>
<td>Years of illness: mean ± SD</td>
<td>17.6 ± 12.1</td>
<td>18.6 ± 13.6</td>
<td>16.8 ± 10.9</td>
</tr>
</tbody>
</table>

**Use of medication**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants: n (%)</td>
<td>8 (12.3)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Typical antipsychotics: n (%)</td>
<td>17 (26.2)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Atypical antipsychotics: n (%)</td>
<td>24 (36.9)</td>
<td>9 (32.1)</td>
</tr>
<tr>
<td>Mood stabilizers: n (%)</td>
<td>60 (92.3)</td>
<td>25 (69.3)</td>
</tr>
</tbody>
</table>

| SD: standard deviation; a lithium, valproate and carbamazepine alone or in combination; \* p = 0.043 for difference between groups. |

**Table 2. Performance of clinical parameters in identifying the presence of insulin resistance in bipolar disorder patients**

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Sensitivity</th>
<th>Especificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP ATP III definition</td>
<td>64.3</td>
<td>91.9</td>
<td>85.7</td>
<td>77.3</td>
</tr>
<tr>
<td>NCEP ATP III modified definition</td>
<td>78.6</td>
<td>89.2</td>
<td>84.6</td>
<td>84.6</td>
</tr>
<tr>
<td>IDF definition</td>
<td>78.6</td>
<td>86.5</td>
<td>81.5</td>
<td>84.2</td>
</tr>
<tr>
<td>Waist circumference (men &gt; 102 cm, women &gt; 88 cm)</td>
<td>62.1</td>
<td>37.8</td>
<td>50</td>
<td>73.7</td>
</tr>
<tr>
<td>Waist circumference (men &gt; 94 cm, women &gt; 80 cm)</td>
<td>100</td>
<td>16.2</td>
<td>47.5</td>
<td>100</td>
</tr>
<tr>
<td>Fasting glucose (≥ 110 mg/dL)</td>
<td>53.6</td>
<td>94.6</td>
<td>88.2</td>
<td>72.9</td>
</tr>
<tr>
<td>Fasting glucose (≥ 100 mg/dL)</td>
<td>71.4</td>
<td>83.8</td>
<td>76.9</td>
<td>79.5</td>
</tr>
<tr>
<td>Blood pressure (≥ 130 x 85 mmHg)</td>
<td>64.3</td>
<td>70.3</td>
<td>62.1</td>
<td>72.2</td>
</tr>
<tr>
<td>Triglycerides (≥ 150 mg/dL)</td>
<td>64.3</td>
<td>81.1</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>HDL cholesterol (men ≤ 40 mg/dL, women ≤ 50 mg/dL)</td>
<td>71.4</td>
<td>75.7</td>
<td>69</td>
<td>77.8</td>
</tr>
</tbody>
</table>

In the multiple linear regression model, waist circumference (B = 0.014, SE 0.002, t = 6.18, p < 0.001), blood glucose (B = 0.002, SE = 0.0004, t = 5.79, p < 0.001), and systolic (B = 0.006, SE 0.001, t = 4.11, p < 0.001) and diastolic BP (B = 0.011, SE 0.0033, t = 3.32, p = 0.002), were retained as predictors of IR. Age, triglycerides and HDL cholesterol were dropped from the model. The multiple linear regression model explained 67% of the variance in IR.

Finally, we constructed ROC curves for different definitions and for waist circumference. Areas under the curve largely overlapped, and there was no significant difference between the four sets (Figure 1; chi2 = 2.98, df = 3, p = 0.39).
Discussion

In the present study we investigated the prevalence of IR and MS and explored its relationship in patients with bipolar disorder. The prevalence of MS was similar to previous reports\(^{25,35}\) and we also found a comparable rate of IR in this population of BD patients. Current MS definitions (NCEP-ATP III, NCEP-ATP III modified and IDF) and each of their components differed in terms of sensitivity and specificity to detect IR. NCEP-ATP III modified criteria were the MS definition most closely associated with IR, with the best trade-off between sensitivity and specificity, maximizing the clinical utility of MS criteria. Waist circumference was the strongest clinical parameter associated with IR in this population of BD patients.

Although widely used in clinical and research contexts almost interchangeably, some studies in non-psychiatric populations have investigated the association of current MS definitions and IR and have found varying sensitivity among different criteria. Hsieh et al.\(^{23}\) applied the modified NCEP-ATP III criteria and found a sensitivity of 47% and a positive predictive value of 64.8% to detect IR by the steady-state plasma glucose concentration (SSPGC). Similar patterns of dissociation between the diagnosis of the MS and IR have been consistently demonstrated in other studies\(^{24-26}\). Sierra-Johnson et al.\(^{27}\) studied a well-defined white non-Hispanic population and found similar results using the same criteria for the MS and the frequently sampled intravenous glucose tolerance test. Using ROC analysis, waist circumference alone was a better predictor of IR than the diagnosis of the MS; the same findings were reported by Wahrenberg et al.\(^{28}\) in healthy volunteers.

The clinical importance of waist circumference as a unique indicator of body fat distribution has been repeatedly stressed\(^{29}\). Even modest reductions of abdominal adiposity have been associated with improvement in several cardiometabolic risk factors, including hyperinsulinemia\(^{30}\). The replication of waist circumference as a strong correlate of IR in our sample is relevant, as different criteria may have found varying sensitivity among different criteria. Hsieh et al.\(^{23}\) in healthy volunteers.

ROC: receiver operator characteristics; AUC: area under the curve; ATP III: National Cholesterol Educational Program – Treatment Adult Panel III criteria; ATP IIM: National Cholesterol Educational Program – Treatment Adult Panel III modified criteria; IDF: International Diabetes Federation criteria.

Figure 1. ROC curves and AUC of three definitions of the metabolic syndrome and waist circumference.

ROC: receiver operator characteristics; AUC: area under the curve; ATP III: National Cholesterol Educational Program – Treatment Adult Panel III criteria; ATP IIM: National Cholesterol Educational Program – Treatment Adult Panel III modified criteria; IDF: International Diabetes Federation criteria.

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Potential conflicts of interest

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