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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Received: 5/15/2009 – **Accepted:** 8/5/2009

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 Clínicas 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.

Gomes FA, et al. / Rev Psiq Clín. 2010;37(2):81-4

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 Clínicas de Porto Alegre, Brasil. 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); do NCEP-ATP III modificado e da International Diabetes Federation (IDF). **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 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. A circunferência da cintura foi o parâmetro clínico mais associado à 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.

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

Introduction

The insulin resistance syndrome was first proposed by Reaven[1] 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 cancer[2] but also to impairment of functioning and cognitive decline[3]. 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 components, 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 levels[4-6]. Increased intra-abdominal fat, as measured by waist circumference, have been consistently regarded as an important contributor to IR in several studies[7-9].

Bipolar disorder (BD) is associated with increased morbidity and mortality due to general medical conditions such as cardiovascular disease, obesity and diabetes[10,11]. 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

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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, Stemmle *et al.*[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[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[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)[21]. The HOMA-IR was calculated as [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[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)[4], NCEP-ATP III modified criteria[5] and International Diabetes Federation (IDF)[6].

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

Variable	All patients (n = 65)	Insulin-resistant (n = 28)	Non insulin-resistant (n = 37)
Age: mean ± SD*	45.6 ± 12.4	49.1 ± 12.9	42.9 ± 11.5
Female sex: n (%)	45 (69.2)	20 (71.4)	25 (67.6)
Years of education: mean ± SD	9.2 ± 4.2	8.5 ± 4.6	9.6 ± 3.9
Years of illness: mean ± SD	17.6 ± 12.1	18.6 ± 13.6	16.8 ± 10.9
Use of medication			
Antidepressants: n (%)	8 (12.3)	4 (14.3)	04 (10.8)
Typical antipsychotics: n (%)	17 (26.2)	7 (25)	10 (27)
Atypical antipsychotics: n (%)	24 (36.9)	9 (32.1)	15 (40.5)
Mood stabilizera: n (%)	60 (92.3)	25 (89.3)	35 (94.6)

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

Clinical parameter	Sensitivity	Especificity	Positive predictive value	Negative predictive value
NCEP ATP III definition	64,3	91,9	85,7	77,3
NCEP ATP III modified definition	78,6	89,2	84,6	84,6
IDF definition	78,6	86,5	81,5	84,2
Waist circumference (men > 102 cm, women > 88 cm)	82,1	37,8	50	73,7
Waist circumference (men > 94 cm, women > 80 cm)	100	16,2	47,5	100
Fasting glucose (≥ 110 mg/dL)	53,6	94,6	88,2	72,9
Fasting glucose (≥ 100 mg/dL)	71,4	83,8	76,9	79,5
Blood pressure (≥ 130 x 85 mHg)	64,3	70,3	62,1	72,2
Triglycerides (≥ 150 mg/dL)	64,3	81,1	72	75
HDL cholesterol (men ≤ 40 mg/dL, women ≤ 50 mg/dL)	71,4	75,7	69	77,8

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).

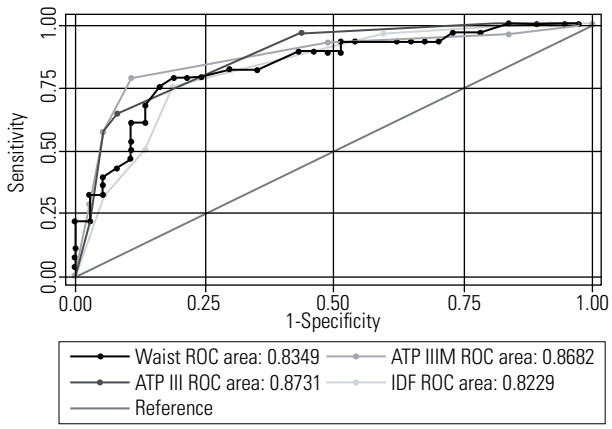

Figure 1. ROC curves and AUC of three definitions of the metabolic syndrome and waist circumference.
ROC: receiver operator characteristics; AUC: area under the curve; ATP III: National Cholesterol Educational Program – Treatment Adult Panel III criteria; ATP IIIM: National Cholesterol Educational Program – Treatment Adult Panel III modified criteria; IDF: International Diabetes Federation criteria.

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[12-13] 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 be more prevalent and contribute in more significant ways to MS diagnosis in different patient populations[13,31].

There is a well-known association of severe mental illness and metabolic abnormalities[32]. Some recent studies have also emphasized the relevance of the problem in Brazil, particularly in psychotic disorders[33,34]. Teixeira and Rocha[12], applying NCEP-ATP III criteria, found elevated rates of MS in psychiatric inpatients with schizophrenia (40%) BD (42.9%) and major depressive disorder (52.9%). Our results not only are in line with these findings but also suggest that some of the clinical features of the metabolic syndrome, particularly waist circumference, are closely related to IR in this patient population.

Only a few studies have investigated the prevalence and clinical correlates of IR in BD. Hung *et al.*[16] found an association between two correlates of IR in non-obese males with BD. Insulin sensitivity was significantly lower and acute insulin response to intravenous glucose was significantly higher in this population and there was an inverse correlation of depressive symptoms and insulin sensitivity. Stemmle *et al.*[17] studied a small sample of unmedicated depressed women with BD. They found increased rates of IR (estimated by the HOMA-IR), obesity and hyperlipidemia in untreated patients and suggested that the metabolic dysfunctions may, at least in part, be attributable to the disorder itself.

Recent findings on the pathophysiology of BD underscore the relevance of studying IR and metabolic abnormalities in this population. Disturbances in metabolic pathways such as insulin-mediated glucose homeostasis, overactivation of the hypothalamic-pituitary-adrenal axis, dysregulated immune and inflammatory processes and adipocytokines profiles are present during both mood episodes and remission[35]. Such deleterious alterations in key adaptive mechanisms may explain some of the complex interactions between bipolar disorder, common general medical conditions and resilience to mood episodes and life events[36].

This study has some limitations and must be interpreted with caution. We studied a relatively small sample and all patients were on psychotropic medications, most on more than one, and some may have an effect on insulin resistance[37], although we found no difference between IR and non-IR patients regarding medication status (Table 1). Due to the older age and long duration of illness these patients may not be representative of the general bipolar population and thus of the whole spectrum of BD and are more likely to represent those typically seen in tertiary care facilities. Another limitation of our study is the lack of a control group of non-medicated individuals. This shortcoming precludes us to conclude whether the metabolic findings are due to the disease itself or to pharmacologic treatments. Longitudinal studies with larger number of patients in different treatment regimens are necessary to address these issues.

Conclusion

IR is associated with several metabolic abnormalities such as impaired glucose homeostasis, dyslipidemia, endothelial dysfunction and inflammation[38], which may in turn be related to future complications such as cardiovascular disease and cognitive deficits usually seen in BD[35,36]. This report shows that the use of different MS criteria in patients with BD may have implications for the detection of insulin resistance, and two conclusions follow directly. Firstly, reasonable sensitivity and specificity can be achieved with currently used criteria. And secondly, waist circumference was the clinical criteria most associated with IR reflecting the relevance of abdominal obesity in this patient population.

Acknowledgments

This study was supported by FIPE-HCPA (GPPG 06-245), Porto Alegre, Brazil.

Potential conflicts of interest

Flávio Kapczinski has received research grants from FIPE-HCPA, National Counsel of Technological and Scientific Development (CNPq), Stanley Foundation, and NARSAD. He has participated in continuous medical education from Lilly, AstraZeneca and Janssen and has served as a consultant/advisory board for Servier. The other authors declare no potential conflicts of interest.

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