Adipokines, metabolic dysfunction and illness course in bipolar disorder

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ABSTRACT

Replicated evidence indicates that individuals with BD are differentially affected by metabolic comorbidities and that its occurrence is a critical mediator and/or moderator of BD outcomes. This study aimed to explore the role of adipokines on bipolar disorder (BD) course and its relationship with metabolic comorbidities (i.e. type 2 diabetes mellitus, obesity). We measured plasma levels of adiponectin and leptin, as well as anthropometric and metabolic parameters of 59 patients with BD and 28 healthy volunteers. Our results showed that, in female participants, adiponectin was lower in individuals with BD, relative to healthy controls ($p = 0.017$). In the BD population, adiponectin levels were correlated with fasting glucose ($r = -0.291$, $p = 0.047$), fasting insulin ($r = -0.332$, $p = 0.023$), C-peptide ($r = 0.040$, $p = 0.040$), homeostatic model assessment-insulin resistance ($r = -0.411$, $p = 0.004$), HDL ($r = 0.508$, $p < 0.001$), VLDL ($r = -0.395$, $p = 0.005$) and triglycerides ($r = -0.310$, $p = 0.030$). After adjustment for age, gender and BMI, individuals with BD and low adiponectin levels (i.e. < 7.5 µg/ml), had a higher number of mood episodes ($p < 0.001$), lower number of psychiatric hospitalizations ($p = 0.007$), higher depressive symptoms ($p < 0.001$) and lower levels of functioning ($p = 0.020$). In conclusion, adiponectin levels, either directly or as a proxy of metabolic dysfunction, is independently associated with an unfavorable course of illness in BD.

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1. Introduction

Accumulating evidence indicates that bipolar disorder (BD) is frequently associated with metabolic disorders, including, but not limited to, obesity, type 2 diabetes mellitus (T2DM) and dyslipidemia (Crump et al., 2013; Czepielewski et al., 2013; Fagiolini et al., 2005; Gomes et al., 2013; Kemp et al., 2014; McIntyre et al., 2010; Perugi et al., 2015; Sicras et al., 2008; Vancampfort et al., 2013). It has been suggested that metabolic comorbidities are critical mediators and/or moderators of BD outcomes (Brietzke et al., 2011; Mansur et al., 2015). For example, replicated evidence indicates

that obesity, insulin resistance (IR) and T2DM are associated with unfavorable illness course characteristics (e.g. depression prone illness; treatment resistance, poor functionality) (Calkin et al., 2009, 2013, 2015; Goldstein et al., 2011; Kemp et al., 2010; McIntyre et al., 2008; Ruzickova et al., 2003).

In addition, a robust body of evidence indicates that, for a subset of individuals with BD, the illness follow a progressive trajectory, characterized by incremental chronicity, treatment resistance and cognitive deficits along the course of several mood episodes (Berk et al., 2014; Kapczinski et al., 2014). These findings have supported the neuroprogression hypothesis, wherein different stages of BD would be associated with distinct neurobiological underpinnings (Berk et al., 2011; Gama et al., 2013; Schneider et al., 2012). For example, a longer illness duration and/or higher number of mood episodes have been associated with increased

inflammatory activation (Panizzutti et al., 2015; Reininghaus et al., 2014), hypothalamic-pituitary-adrenal axis dysfunction (Fries et al., 2014) and higher brain-derived neurotrophic factor (BDNF) levels (Munkholm et al., 2015).

Adipokines, such as leptin and adiponectin, are critical mediators of energy homeostasis. Both leptin and adiponectin have endocrine functions and are involved in glucose and insulin regulation, lipoproteins homeostasis and inflammatory activity (Christou and Kiortsis, 2013; Esmaili et al., 2014; Ouchi et al., 2011). Abnormal levels of circulating adipokines have been reported in BD clinical populations (Atmaca et al., 2002b; Barbosa et al., 2012; Elmslie et al., 2009; Kurt et al., 2007; Tsai et al., 2007). The foregoing findings persist after adjusting for demographic factors and for the presence of obesity providing a rationale for hypothesizing that adipokines are relevant to the mechanistic substrates of BD (Barbosa et al., 2012; Soeiro-de-Souza et al., 2014). Moreover, evidence has indicated that a higher number of mood episodes is also associated with a higher frequency of chronic medical conditions, independently of age (Lackner et al., 2015; Magalhaes et al., 2012), suggesting that metabolic processes, including but not limited to adipokines signaling, may be relevant mediators of illness progression (Brietzke et al., 2011; Lackner et al., 2015; Magalhaes et al., 2012). However, to our knowledge, only one study has reported on the impact of adipokines on illness course variables, failing to find any significant associations (Barbosa et al., 2012).

Herein, we aimed to explore the role of adipokines on BD course and its relationship with metabolic comorbidities. We hypothesized that: (1) adiponectin and leptin levels are significantly different amongst individuals with BD and healthy controls; (2) adipokines levels would be correlated with metabolic parameters in the BD population; and (3) adipokines levels would moderate BD course and severity.

2. Material and methods

2.1. Study population and clinical assessment

This study was approved by the local ethics committee and all subjects provided written informed consent before any study procedure. Patients (N = 59) with BD type I/II were recruited from the Vila Maria Outpatient Clinic in São Paulo, Brazil. A comparison group of healthy volunteers (N = 28) was also recruited from the community, through advertisements. Psychiatric diagnosis was confirmed with the Structured Clinical Interview for DSM-IV (SCID-I). Manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HDRS), respectively; functioning was assessed using the Global Assessment of Functioning (GAF) Scale. All subjects were inquired on medical history, including lifetime use of any medication. We categorized, for the purposes of this study, the currently used psychotropic medications based on class (e.g. second-generation antipsychotics, anticonvulsants) and on potential of drug-induced weight gain, as follows: (1) minimal effect: high-potency first-generation antipsychotics, selective serotonin reuptake inhibitors, bupropion, aripiprazole, lamotrigine; (2) moderate effect: lithium, valproate, tricyclic antidepressants, risperidone and (3) marked effect: quetiapine, olanzapine, low-potency first-generation antipsychotics (Correll et al., 2015; Henderson et al., 2015). Body mass index (BMI) was also measured using the formula BMI = weight (kg)/height (meters)^2. The healthy volunteers comparison group was screened for psychiatric disorders using SCID-I. Healthy subjects were not prescribed psychotropic medication, and had no history of major psychiatric disorders, dementia or mental retardation. Exclusion criteria included presence of unstable or acute medical conditions and current or lifetime alcohol or drug abuse. Individuals prescribed medications that impact metabolic parameters (e.g. antidiabetic medications, statins) were excluded from this analysis.

2.2. Laboratory assessment

Whole blood samples were obtained from all participants by arm venipuncture between 8:00 to 10:00am, after a 12 h fasting. Metabolic parameters were measured immediately in a single laboratory with the same assay. We estimated IR using the homeostatic model assessment-insulin resistance (HOMA-IR) equation: HOMA-IR = fasting plasma glucose (mg/dl)/fasting serum insulin (μU/mL)/405. The HOMA is an accepted measure of IR that correlates well with estimates using the gold-standard euglycemic clamp method (Katsuki et al., 2001; Wallace et al., 2004).

Blood collected in EDTA tubes were kept in ice until processing, for plasma isolation EDTA tubes were centrifuged at 1500 rpm for 5 min in a refrigerated centrifuge, aliquoted and kept at −80 °C until further analyzed. Adiponectin and leptin plasma levels were determined by enzyme-linked immunosorbent assay (ELISA) kit (EMD Millipore Corporation, USA. Cat. #EZHADP-61K and #EZHL-80SK, respectively), according to the manufacturer's instructions. The laboratory staff responsible for analyses were blinded to group. Optical density was read with a microtitre plate photometer at 450 nm. Concentration was determined by interpolation from a standard curve prepared with standard samples supplied by the manufacturer and expressed in μg/mL or ng/mL. Samples and quality controls were run in duplicate, if the coefficient of variation between the replicates was higher than 10%, the sample was repeated. There were no undetectable values. For leptin the intra-assay (n = 92) coefficient of variability (CV) was 4.5%, the inter-assay CV (n = 3) was 4.33%. For adiponectin, values were 3.38% (n = 89) and 10.99% (n = 3), respectively.

2.3. Statistical analyses

For statistical analysis, SPSS software for Windows (version 17.0) was used. For the comparison of the demographic and clinical data, the independent samples t-test was used for quantitative variables; the Chi-square test was used for categorical variables. Generalized linear models were used to compare adipokines levels between individuals with BD and healthy controls, as well as to assess the relationship between adiponectin and continuous clinical outcomes. We used linear, Poisson (for count data, e.g. number of episodes) and gamma (for positively skewed distribution, e.g. adiponectin and leptin levels) distributions, as appropriate. For dichotomous outcomes we used logistic regression. All analyses included age, gender and BMI as covariates.

3. Results

3.1. Sample characteristics

Of the 59 recruited individuals with BD, 53 (88.3%) were diagnosed with BD type 1 and 7 (10.1%) with BD type 2. The mean age was 43.10 years (SD 10.26); 46 participants were female (78.0%) and 35 (59.3%) were Caucasian. The mean BMI was 28.95 (SD 5.16), 18 (30.5%) subjects were obese (BMI ≥ 30). There was no statistical differences in age (p = 0.124), gender (p = 0.084) or BMI (p = 0.091) between subjects with BD and healthy controls.

Forty-one (69.5%) individuals with BD were euthymic at the time of the assessment, the remaining 18 (30.5%) fulfilled criteria for a depressive episode. No subjects fulfilled criteria for a manic or mixed episode. The mean YMRS score was 1.68 (SD 2.93), the mean HDRS score was 5.25 (SD 5.25) and the mean GAF score was 74.81