Journal of Affective Disorders 222 (2017) 185–194

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

# Indices of insulin resistance and glucotoxicity are not associated with bipolar disorder or major depressive disorder, but are differently associated with inflammatory, oxidative and nitrosative biomarkers

Kamila Landucci Bonifácio[a,c], Décio Sabbatini Barbosa[a,c,i], Estefânia Gastaldello Moreira[c], Carine Coneglian de Farias[a,c], Luciana Higachi[a,c], Alissana Ester Iakmiu Camargo[a], Janaina Favaro Soares[a], Heber Odebrecht Vargas[d], Sandra Odebrecht Vargas Nunes[c], Michael Berk[e,f,g,h,*], Seetal Dodd[e,f,g], Michael Maes[b,e,*]

[a] Laboratory of Graduation Research, State University of Londrina, University Hospital, Londrina, Paraná, Brazil
[b] Department of Psychiatry, Chulalongkorn University, Bangkok, Thailand
[c] Graduation Program in Health Sciences, State University of Londrina, Londrina, PR, Brazil
[d] Department of Psychiatry, Health Sciences Center, State University of Londrina, Londrina, Paraná, Brazil
[e] Deakin University, IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Australia
[f] Oygen, the National Centre of Excellence in Youth Mental Health, Parkville, Australia
[g] Department of Psychiatry, University of Melbourne, Australia
[h] The Florey Institute for Neuroscience and Mental Health, University of Melbourne, Australia
[i] Department of Clinical Analysis and Toxicological, State University of Londrina, Brazil

ARTICLE INFO

*Keywords:*
Insulin resistance
Depression
Mania
Bipolar disorder
Oxidative stress
Inflammation

ABSTRACT

*Background:* Insulin resistance (IR) is a key factor in diabetes mellitus, metabolic syndrome (MetS) and obesity and may occur in mood disorders and tobacco use disorder (TUD), where disturbances of immune-inflammatory, oxidative and nitrosative stress (IO & NS) pathways are important shared pathophysiological pathways.
*Methods:* This study aimed to a) examine IR and β-cell function as measured by the homeostasis model assessment of insulin resistance (HOMA-IR) and insulin sensitivity and β cell function (HOMA-B) and glucotoxicity (conceptualized as increased glucose levels versus lowered HOMA-B values) in 74 participants with major depressive disorder (MDD) and bipolar disorder, with and or without MetS and TUD, versus 46 healthy controls, and b) whether IR is associated with IO & NS biomarkers, including nitric oxide metabolites (NOx), lipid hydroperoxides (LOOH), plasma advanced oxidation protein products (AOPP), C-reactive protein (CRP), haptoglobin (Hp) and uric acid.
*Results:* Mood disorders are not associated with changes in IR or glucotoxicity, although the number of mood episodes may increase IR. 47.8% of the variance in HOMA-IR is explained by AOPP and body mass index (BMI, both positively) and NOx, Hp and TUD (all inversely). 43.2% of the variance in HOMA-B is explained by NOx, Hp and age (all inversely associated) and higher BMI and sex. The glucotoxic index is strongly associated with NOx, Hp and BMI (positively), male gender and lower education.
*Limitations:* This is a cross-sectional study and therefore we cannot draw firm conclusions on causal associations.
*Conclusions:* Activated IO & NS pathways (especially increased Hp and NOx) increase glucotoxicity and exert very complex effects modulating IR. Mood disorders are not associated with increased IR.

## 1. Introduction

Chronic hyperglycemia ("glucotoxicity") may induce damage in insulin-target tissues and pancreatic β-cells leading to insulin resistance, which is a key factor in diabetes mellitus, metabolic syndrome (MetS) and obesity (He et al., 2014; Kulkarni et al., 2014). Insulin resistance may occur in mood disorders, either major depressive disorder (MDD) or bipolar disorder (BD) (Sharma et al., 2014; Shen and Bergquist-Beringer, 2013). MDD and BD patients have been reported to have a 3–5 times higher risk of developing diabetes mellitus type 2 (T2DM) than the general population, although there are negative reports on the association between mood disorders and diabetes (Jacka

* Corresponding author.
*E-mail addresses:* mikebe@barwonhealth.org.au (M. Berk), dr.michaelmaes@hotmail.com (M. Maes).

http://dx.doi.org/10.1016/j.jad.2017.07.010
Received 30 January 2017; Received in revised form 28 June 2017; Accepted 5 July 2017
Available online 06 July 2017
0165-0327/ 

et al., 2007; Rasgon and Jarvik, 2004). Both disorders may be accompanied by disturbances in glucose homeostasis, higher body mass index (BMI) and insulin resistance (Carvalho et al., 2014; Kan et al., 2013; Rasgon and Jarvik, 2004; Sharma et al., 2014). For example, Calkin et al. (2015) (Calkin et al., 2015) found that insulin resistance and T2DM are common among BD patients and are associated with an unfavorable clinical course and poor treatment outcome (Kan et al., 2013). However, other authors found no significant association between MDD and insulin resistance, suggesting that the association between MDD and T2DM observed in previous studies may be mediated through other pathways (Shen and Bergquist-Beringer, 2013).

Smoking and tobacco use disorder (TUD) are associated with hyperinsulinemia and insulin resistance in some (Wang et al., 2015), but not all, studies (Bortolasci et al., 2015). Smokers exhibit several aspects of the insulin resistance syndrome and are at increased risk (around 1.5-fold) for T2DM (Onat et al., 2007). Moreover, there is some evidence that cigarette smoking could acutely impair insulin action in normal subjects and T2DM patients, whilst clinical studies have shown negative effects of smoking on β-cell functions (Liu et al., 2011). A robust comorbidity between mood disorders and TUD and evidence for a bidirectional relationship between both disorders exists, suggesting that both mood disorders and TUD may together aggravate insulin resistance (Bortolasci et al., 2015; Moylan et al., 2015; Nunes et al., 2013; Stafford et al., 2013).

Several factors underpin the pathophysiology of insulin resistance, including hyperinsulinemia, higher BMI, lipotoxicity, hyperlipidemia, genetics and aging and activated immune-inflammatory, oxidative and nitrosative stress (IO & NS) pathways (Fabbrini et al., 2014; Ye, 2011). A significant association between oxidative stress and insulin resistance has been observed in individuals with impaired fasting glucose (Kulkarni et al., 2014; Meigs, 2007). Furthermore, obese subjects show increased levels of inflammatory markers and acute-phase reactants, including C-reactive protein (CRP) and haptoglobin (Hp), which are both associated with T2DM (Chen et al., 2015; Maffei et al., 2016).

MDD and BD are now conceptualized at least in part as neuro-immune, neuro-oxidative and neuro-nitrosative disorders (Berk et al., 2013; Maes, 1995; Moylan et al., 2014). Both mood disorders are characterized by increased levels of CRP, Hp, pro-inflammatory cytokines, and activated O & NS pathways, including increased reactive oxygen radicals (ROS), leading to oxidative damage to lipids and proteins (Maes, 1995; Maes et al., 2011; Moylan et al., 2014).

Importantly, chronically activated immune-inflammatory pathways may lead to insulin resistance and β-cell dysfunction, thereby increasing risk towards T2DM (Kan et al., 2013). Inflammation is an important component linking insulin resistance with nutrient overload and increased visceral adipocyte mass. In the insulin-sensitive state, insulin binding to its receptor results in downstream insulin signaling (Schenk et al., 2008), whereas in the insulin-resistance state, pro-inflammatory molecules activate various kinases (Hameed et al., 2015), which inhibit insulin action in the insulin signaling pathway (Schenk et al., 2008). There may be direct mechanistic links between O & NS and the pathogenesis of insulin resistance through accumulation of O & N damage to critical macromolecules in insulin-sensitive tissues and the direct effects of advanced oxidation protein products (AOPPs) and lipid hydroperoxides (LOOH) (Tangvarasittichai, 2015; Venturini et al., 2015). Hyperglycemia-induced oxidative stress exerts a direct negative effect on β-cell function (Kulkarni et al., 2014). There is a significant association between increased nitrosylation of proteins in insulin-sensitive tissues and obese or insulin-resistant phenotypes (Styskal et al., 2012). Smoking and TUD activate IO & NS pathways (Berk et al., 2013; Moylan et al., 2014) and thus may contribute to insulin resistance and β-cell dysfunction. Another factor related to the onset of insulin resistance is increased uric acid, which may enhance oxidative stress in mitochondria (Lanaspa et al., 2012), cause oxidative stress in islets cells with consequent islet cell dysfunction (Roncal-Jimenez et al., 2011) and may induce inflammatory responses in adipose cells thereby lowering adiponectin production (Baldwin et al., 2011).

Based on the above considerations, this study in patients with MDD and BD aimed to examine: a) insulin resistance and β-cell function, as measured by homeostasis model assessments based on plasma glucose and insulin levels, in patients with mood disorders with and without MetS and TUD; b) the association between insulin resistance and β-cell function and IO & NS biomarkers, including CRP, Hp, nitric oxide metabolites (NOx), AOPPs and LOOH; and c) whether insulin and glucose levels are related to mood disorders, IO & NS biomarkers, TUD, MetS and uric acid. The hypothesis was that indices of insulin resistance and glucotoxicity would be related to mood disorders, TUD, uric acid and IO & NS biomarkers.

## 2. Methods

### 2.1. Subjects

In this study, patients with BD (n = 47) and MDD (n = 27) were recruited from the Psychiatric Outpatient Ambulatory at the State University of Londrina (UEL). The control group (n = 46) was recruited from the same catchment area. All participants aged 18–65 years and no criteria for gender and ethnicity were settled. Exclusion criteria for patients were a) cognitive impairment including mental retardation and any other cognitive disorders that would compromise the understanding of the study terms and conditions; and b) other current or lifetime diagnoses of axis-I diagnoses, including schizophrenia, psychoorganic syndromes and dementia. Exclusion criteria for controls were any current or lifetime axis-I diagnoses. Exclusion criteria for both patients and controls were pregnancy, inflammatory or (auto) immune disorders, including chronic obstructive pulmonary disorder, hepatitis and acquired immunodeficiency syndrome; and use of immunomodulatory drugs or antioxidant supplements. All subjects gave written informed consent to participate in the study after the approval of this research by the Ethics Research Committee at UEL (number CAAE 34935814.2.0000.5231).

### 2.2. Diagnostic procedures and measurements

MDD and BD were diagnosed at interview by a trained psychiatrist using the semi-structured DSM-IV interview (SCID) translated and validated in Portuguese (Del-Ben et al., 2001). A translated and validated version of the Hamilton Depression Rating Scale (HAM-D) (Moreno and Moreno, 1998) was used to measure severity of depression. The severity of manic symptoms was measured using the Young Mania Rating Scale (YMRS) (Vilela et al., 2005). We used the Hamilton Anxiety Rating Scale (HAM-A) to measure severity of anxiety (Hamilton, 1959). Nicotine dependence or tobacco use disorder (TUD) was diagnosed using criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2000). The severity of TUD was estimated using the Fagerström Nicotine Dependence Scale. This instrument was translated and adapted to the Portuguese language (Carmo and Pueyo, 2002). We used the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) questionnaire to screen for risk of alcohol and hypnotics abuse. This test was translated and adapted to Portuguese by Henrique et al., 2004 (Henrique et al., 2004). In all participants and controls, a semi-structured questionnaire was used to collect clinical and socio-demographic data, including age, gender, marital status, ethnicity, educational background, employment status, use of psychotropic drugs, and use other medicines.

### 2.3. Anthropometric and blood pressure measurements

We measured waist circumference during expiration, in a standing and relaxed position, at the midline between the lower costal margins and the iliac crest parallel to the floor. We measured systolic and diastolic blood pressure using a mercury sphygmomanometer on the right