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Research report

Factors influencing insulin resistance in relation to atherogenicity in mood disorders, the metabolic syndrome and tobacco use disorder

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ABSTRACT

Objective: This study examines the effects of malondialdehyde (MDA) and uric acid on insulin resistance and atherogenicity in subjects with and without mood disorders, the metabolic syndrome (MetS) and tobacco use disorder (TUD).
Methods: We included 314 subjects with depression and bipolar depression, with and without the MetS and TUD and computed insulin resistance using the updated homeostasis model assessment (HOMA2IR) and atherogenicity using the atherogenic index of plasma (AIP), that is log10 (triglycerides/high density lipoprotein (HDL) cholesterol.
Results: HOMA2IR is correlated with body mass index (BMI) and uric acid levels, but not with mood disorders and TUD, while the AIP is positively associated with BMI, mood disorders, TUD, uric acid, MDA and male sex. Uric acid is positively associated with insulin and triglycerides and negatively with HDL cholesterol. MDA is positively associated with triglyceride levels. Comorbid mood disorders and TUD further increase AIP but not insulin resistance. Glucose is positively associated with increasing age, male gender and BMI.
Discussion: The results show that mood disorders, TUD and BMI together with elevated levels of uric acid and MDA independently contribute to increased atherogenic potential, while BMI and uric acid are risk factors for insulin resistance. The findings show that mood disorders and TUD are closely related to an increased atherogenic potential but not to insulin resistance or the MetS. Increased uric acid is a highly significant risk factor for insulin resistance and increased atherogenic potential. MDA, a marker of lipid peroxidation, further contributes to different aspects of the atherogenic potential. Mood disorders and TUD increase triglyceride levels, lower HDL cholesterol and are strongly associated with the atherogenic, but not insulin resistance, component of the MetS.

List of abbreviations: AIP, atherogenic index of plasma; BMI, body mass index; CVD, cardiovascular disease; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; ELISA, enzyme-linked immunosorbent assay; HDL-c, high-density lipoprotein; HDRS, Hamilton Depression Rating Scale; HOMA2B%, homeostasis model assessment of β-cell function; HOMA2IR, homeostasis model assessment of insulin resistance; HOMA2S%, homeostasis model assessment of insulin sensitivity; LDL-c, low-density lipoprotein; MDA, malondialdehyde; MEIA, microparticle enzyme immunoassay; MetS, metabolic syndrome; OS, oxidative stress; TG, triglycerides; TUD, tobacco use disorder

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1. Introduction

There is a significant comorbidity between mood disorders, either bipolar disorder or depression, the metabolic syndrome (MetS) and tobacco use disorder (TUD) (Vargas et al., 2014). The MetS is the clustering of an increased atherogenic lipid profile [e.g. hypertriglyceridemia and decreased high-density lipoprotein cholesterol (HDL-c)], insulin resistance, abdominal obesity and elevated blood pressure (Jamshidi et al., 2014). The MetS and related atherogenicity and insulin resistance are strongly related to an increased risk of diabetes type 2 and cardiovascular disease (CVD) (Jamshidi et al., 2014). Disorders of lipoprotein metabolism may account for around 50% of the population-attributable risk of developing CVD (Millan et al., 2009). Insulin resistance is defined as a condition in which insulinsensitive target tissues, including adipose tissue, pancreas, skeletal muscles and liver, do not respond adequately to the physiological activities of insulin (Laakso and Kuusisto, 2014). The homeostasis model assessment (HOMA) and the updated HOMA2 model offer methods to measure insulin resistance (HOMA2IR), insulin sensitivity (HOMA2S%) and beta-cell function (HOMA2B%) based on fasting plasma levels of glucose and insulin (Matthews et al., 1985). The use of the atherogenic index of plasma (AIP) and Castelli risk index 1 and 2 significantly predict vascular risk with a predictive value greater than the isolated lipid variables (Millan et al., 2009; Nunes et al., 2013). The AIP is computed as log10 triglyceride/HDL-c (Vargas et al., 2014) and reflects the presence of atherogenic small low-density lipoprotein cholesterol (LDL-c) and HDL-c particles in plasma and is a sensitive predictor of coronary atherosclerosis and CVD risk (Onyedum et al., 2014).

Patients with bipolar disorder and major depressive disorder show an increased mortality and morbidity due to CVD (Assies et al., 2014). A review, systematic review and meta-analysis showed a small but significant association between insulin resistance and depressive symptoms (pooled effect size 0.19, 95% CI 0.11–0.27) (Silva et al., 2012; Kan et al., 2013). There is a robust comorbidity between mood disorders and TUD and evidence for a bidirectional relationship between both disorders (Nunes et al., 2013). TUD increases risk of the MetS and insulin resistance and causes an atherogenic lipid profile (Bortolasci et al., 2014; Jamshidi et al., 2014). TUD leads to increased mortality (Ezzati and Lopez, 2003) and is one of the major risk factors for multiple chronic diseases, including CVD (Gellert and Scho, 2014).

Activated immune-inflammatory, oxidative and nitrosative stress (IO&NS) pathways and a pro-atherogenic lipid profile are found in mood disorders (either depression or bipolar disorder), the MetS, and TUD. Thus, these three conditions are accompanied by increased levels of pro-inflammatory cytokines, including interleukin (IL)-1β and IL-6, lipid peroxidation biomarkers, including malondialdehyde (MDA), and lowered levels of HDL-c and increased atherogenic indexes, including Castelli risk indexes 1 and 2 and AIP (Maes et al., 1994, 1997, 2011; Vargas et al., 2013; Nunes et al., 2014). Cigarettes contain a significant number of compounds that produce oxidative stress generating MDA through lipid peroxidation (Berger et al., 2014). Recently, we have reviewed that the comorbidities between mood disorders and TUD (Nunes et al., 2013), mood disorders and the MetS/CVD (Maes et al., 2011; Vargas et al., 2013) and TUD and the MetS/CVD (Nunes et al., 2013) may be explained by shared IO&NS pathways and atherogenic changes in lipid profile. Shared metabolic risk factors between mood disorders and the MetS/CVD are lowered serum levels of HDL-c and disorders in the reverse transport of cholesteryl esters (Maes et al., 1994; 2011; Maes and Smith 1998; Nunes et al., 2014). Oxidative stress is related to the development of hyperlipidemia (Ibrahim et al., 1997) and treatment with antioxidants may decrease MDA levels in association with improving triglyceride and total cholesterol levels (Zhao et al., 2014). Oxidative stress may oxidize HDL-c which may have adverse consequences because HDL-c has anti-inflammatory, antioxidant and antithrombotic properties and additionally transports excess cholesterol to the liver (the reverse cholesterol transport) thus decreasing cholesterol load and causing vascular inflammation (Linsel-Nitschke and Tall, 2005; He et al., 2013). This is concordant with the fact that MDA levels are associated with increased atherogenic lipid risk factors (Manohar et al., 2013). The exact relationships between mood disorders, insulin resistance and atherogenic indexes (after controlling for the effects of body mass index (BMI), gender and age) have remained elusive.

Another metabolic biomarker that is associated with the MetS/CVD, insulin resistance, and atherogenecity is uric acid. Epidemiological studies show a significant association between uric acid, insulin resistance and the MetS (Feoli et al., 2014), while the MetS is associated with a very high incidence of hyperuricemia (Facchini et al., 1991; Choi and Ford 2014). Uric acid elevation may be a risk factor for the onset phase of type 2 diabetes (Miyake et al., 2014). Some authors also suggest a relationship between elevated BMI, obesity and insulin resistance and high levels of serum uric acid (Fabbrini et al., 2014). Previous studies found significant positive correlations between uric acid levels and an increased AIP index (Lippi et al., 2010; Baliarsingh et al., 2012) and inverse relationships between uric acid and HDL-c levels (Chu et al., 2000; Lin et al., 2006; Onat et al., 2006a, 2006b). Previous studies showed increased uric acid levels in bipolar disorder (Albert et al., 2015) and lower uric acid in depression (Chaudhari et al., 2010; Wen et al., 2012). Allopurinol, the prototypical uric acid lowering agent, appears to have equivocal effects in mood disorders, with positive and negative trials published (Machado-Vieira et al., 2008; Weiser et al., 2014; Jahangard et al., 2015).

The aims of this study are: (a) to examine insulin resistance, as measured by homeostasis model assessment (HOMA2IR), and the AIP in mood disorders, the MetS and TUD; and (b) to examine the effects of MDA and uric acid on HOMAIR (and insulin and glucose levels) and AIP (and triglyceride and HDL-c levels) in subjects with and without mood disorders, the MetS and TUD. The primary hypothesis is that mood disorders and TUD are significantly associated with the MetS and its components, i.e. insulin resistance and atherogenicity, and that MDA and uric acid are related to both components of the MetS.

2. Subjects and methods

2.1. Subjects

314 subjects, aged 18–65 years and of Caucasian, African, Asian and mixed ethnicity, were enrolled in this study. They were recruited from staff at the State University of Londrina and an outpatient ambulatory of smoking cessation from the same institution, and comprised 120 individuals with mood disorders versus 194 without mood disorders, 224 individuals with MetS and 90 individuals without MetS; and 128 smokers versus 186 non-smokers. The diagnosis of the MetS was made using the diagnostic criteria of the International Diabetes Federation, i.e. 3 of the follow criteria should be present: (a) abdominal obesity (waist circumference $\geq$90 cm for men and $\geq$80 cm for women in South Asian and South Americans and $\geq$94.0 cm for men and $\geq$80.0 cm for women in Caucasians); (b) low HDL-c ($<$40 mg/dL in men and $<$50 mg/dL in women) or on hypolipidemic drugs; (c) hypertriglyceridemia (triglycerides $>$150 mg/dL) or on a hypolipidemic agent; (d) increased fasting glucose ($>$100 mg/dL) or on oral antidiabetic medication; (e) increased average blood pressure (130/85 mm Hg) or currently taking antihypertensive medication (Alberti et al., 2009). 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 arm and used the mean value of two measurements carried