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Research report

Atherogenic index of plasma and atherogenic coefficient are increased in major depression and bipolar disorder, especially when comorbid with tobacco use disorder

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ABSTRACT

Background: There is a robust comorbidity between mood disorders and cardiovascular disorder (CVD). The atherogenic index of plasma (AIP) and the atherogenic coefficient (AC) are important atherogenic indexes. The aims of this study were to delineate whether AIP and AC are increased in mood disorders especially when comorbid with tobacco use disorder (TUD).
Methods: In this case-control study we included 134 patients with mood disorders, bipolar disorder and unipolar depression (cases), and 197 individuals without mood disorder (controls) divided into those with and without TUD (defined as never-smokers). Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLc) and low-density lipoprotein cholesterol (LDLc) were measured. AIP and AC were computed as log (TG/HDLc) and non-HDLc/HDLc, respectively.
Results: The AIP and AC indexes were significantly increased in patients with mood disorders versus controls, both in depression and bipolar disorder. Patients with mood disorder without TUD and patients with TUD without mood disorder showed higher AIP and AC values than never-smokers while those with comorbid mood disorders and TUD showed significantly higher AIP and AC levels than all other individuals. A large part of the variance in the AIC (26.4%) and AC (20.4%) was explained by mood disorders, TUD, male gender and body mass index.
Conclusions: The findings suggest that lipid abnormalities leading to an increased atherogenic potential are involved in the pathophysiology of mood disorders (depression and bipolar disorder) and especially comorbid mood disorder and TUD. The comorbidity between mood disorders and CVD may be partly explained increased through AIP and AC indexes, impacting increments in atherogenic potential.

1. Introduction

Major depressive disorder and cardiovascular disease (CVD) are leading causes of worldwide disability (Lopez et al., 2006). Depressive disorder is highly comorbid with CVD, including heart failure, myocardial infarction, stroke, transient ischemic attack (Musselman et al., 1998; Maes et al., 2011a). Depressive disorders are present in 1 of 5 outpatients with coronary heart disease and in 1 of 3 outpatients with congestive heart failure, and these figures may underestimate the real prevalence as many cases are not recognized (Whooley, 2006; Whooley et al., 2008). Depression is also a risk factor for greater mortality in patients with coronary heart disease (CHD): the risk of mortality is at least two or three times higher for patients who had suffered from CHD with comorbid clinical depression (Lippi et al., 2009).

The shared pathways that underpin the pathophysiology of mood disorders and CDV are not well defined. Activated

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immune-inflammatory and oxidative and nitrosative stress (IO&NS) pathways in depression may increase the risk to develop CVD or may worsen the course of CVD (Maes et al., 2011a). Adverse health behaviors play a role in the association between depressive symptoms and cardiovascular events, especially overweight and obesity and tobacco use disorders (Nunes et al., 2012, 2013a, 2013b, 2014). These commonalities have led for calls for depression to be included among the non-communicable disorders (Jacka et al., 2014).

Nevertheless, dyslipidemia has been identified as one of the most important risk factors associated with CDV. Low high-density lipoprotein cholesterol (HDLc), elevated triglycerides (TG) and high low-density lipoprotein cholesterol (LDLc) levels are associated with the onset of CVD (Weissglas-Volkov and Pajukanta, 2010). The Castelli risk indexes are frequently used in the clinic to predict CVD risk (Millán et al., 2009). Recently, we found that the Castelli risk index is significantly higher in major depressed patients than in controls, whereas patients with bipolar disorder occupied an intermediate position (Vargas et al., 2014). These results underscore that alterations in lipid profile in depression (and possibly not in bipolar disorder) may increase CVD risk and thus underpin the comorbidity between depression and CVD.

Important lipid ratios that are associated with an increased atherogenic potential and may predict CVD risk are the atherogenic index of plasma (AIP) {(logTG)/HDLc} and the atherogenic coefficient (AC) {(Non-HDLc)/HDLc} (Dobiasova and Frohlich, 2000; 2001; Brehm et al., 2004; Bhardwaj et al., 2013). No research has examined whether the AIP index differs between depressed or bipolar patients as compared to normal controls.

The purpose of this study is to delineate whether the atherogenic indexes, i.e. AIP and AC, differed between patients with depression or bipolar disorder and controls; and whether these associations were impacted by the effects of male gender, body mass index or the metabolic syndrome, and tobacco use disorder. The null hypothesis was that the new atherogenic AIP and AC indexes would not differ between patients with depression or bipolar disorder and controls.

2. Methods

2.1. Study population

In this case-control, cross-sectional study we examined subjects with mood disorders ($n=134$) and normal controls ($n=197$) recruited from the staff at Londrina State University (UEL) and an outpatient ambulatory of smoking cessation, UEL, Paraná, Brazil. We included men and women of all ethnicities and aged 18–65 years old. Exclusion criteria were a) subjects with life-time axis-I diagnoses other than mood disorders and tobacco use disorder (e.g. schizophrenia, psycho-organic syndromes); b) cases and controls with abnormal blood tests, such as aspartate transaminase (AST), alanine transaminase (ALT), hemogram, urea and creatinine; c) subjects with medical illness, including (auto)immune disorders, diabetes, inflammatory bowed disease, HIV, hepatitis B and C; and d) individuals who used antioxidant supplements or were treated with immunomodulatory drugs, including glucocorticoids. Controls were excluded for any axis-I diagnoses. 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 250/2010).

2.2. Instruments

The diagnoses mood disorders, major depressive disorder and bipolar disorder, and tobacco use disorder were made by a trained psychiatrist using the semi-structured DSM-IV interview (SCID) axis I (American Psychiatric Association, 2000) translated into Portuguese and validated (Del Ben et al., 2001). A Portuguese translation of the Hamilton Depression Rating Scale (HDRS), 21-item version, was employed to assess symptoms of depression experienced over the past week (Moreno and Moreno, 1998). We included only individuals with current tobacco use disorder versus those who were never-smokers. Tobacco use disorder was defined as individuals who at the time of the interview smoked every day or when cessation of tobacco could produce tobacco withdrawal (American Psychiatric Association, 2000). Never-smokers were individuals without a lifetime diagnosis of tobacco use disorder and who additionally did not smoke one cigarette over their lifetime. Our criteria for never-smokers are thus much more restrictive than former case criteria which defined never-smokers as individuals who smoked less than 100 cigarettes during their lifetime but currently did not smoke (Centers for Disease Control and Prevention, 2011).

A semi-structured questionnaire was used to gather clinical and socio-demographic data, including age, gender, marital status, ethnicity, educational background, employment status, use of psychotropic drugs, and use of statins. We used the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) questionnaire to screen for risk of alcohol in adults. This test was translated and adapted to Portuguese by Henrique et al. (2004).

2.3. Anthropometrics measurements

Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). We used the International Diabetes Federation (IDF) diagnostic criteria to make the diagnosis of metabolic syndrome if at least three criteria out of five were present: 1) abdominal obesity using population and country specific definitions, 2) hypertriglyceridemia: ≥ 150 mg/dl or on hypolipidemic agent, 3) low HDLc: ≤ 40 mg/dl in men and ≤ 50 mg/dl in women or on hypolipidemic agent, 4) average blood pressure $\geq 130/85$ mm Hg or currently taking antihypertensive medication, 5) elevated fasting glucose ≥ 100 mg/dL or on oral antidiabetic medication (Alberti et al., 2005, 2009).

2.4. Laboratory assessments

Blood samples for the determination of serum lipids were collected after an overnight fast (12–14 h). Total cholesterol was assayed using an automated method in a clinical chemistry system (Dimension® RXL, Siemens Healthcare Diagnostics Inc., Newark, DE, USA). HDLc was measured directly with the same methods and without sample pretreatment or centrifugation steps. Triglycerides were assayed using an automated method in a clinical chemistry system (Dimension® RXL, Siemens Healthcare Diagnostics Inc., Newark, DE, USA). The inter-assays CV values for all analytes were $<5.0\%$. LDL cholesterol was calculated using Friedewald's equation, i.e. LDL cholesterol = total cholesterol − HDL cholesterol/triglycerides/5.0 (mg/dL). Consequently, we computed the ACP value as (logTG)/HDL cholesterol and the AC value as total cholesterol − HDL cholesterol/HDL cholesterol.

2.5. Statistical analyses

Differences between study samples in socio-demographic, clinical and metabolic data were assessed using analyses of variance (ANOVAs) or analyses of covariance (ANCOVAs). Fisher's protected least significant difference (LSD) or Tukey test was used to examine multiple comparisons between the study groups. We used analysis of contingency tables (χ^2 test) or Fisher's exact probability test to assess the association between socio-demographic, clinical and anthropometric data and diagnostic groups.