Contents lists available at ScienceDirect

Addictive Behaviors Reports

Depressed female smokers have higher levels of soluble tumor necrosis factor receptor 1

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ABSTRACT

Aim: To examine clinical and biomarkers in depressed female smokers, in order to better clarify the process that link mood disorders, childhood trauma and smoking in women.
Methods: The clinical sample comprised women with unipolar or bipolar depression, divided into subgroups of smokers and never-smoker. The control groups comprised two subgroups non-depressed women, separated into smokers and never-smokers. A structured questionnaire was used to assess socio-demographic and clinical data. The following scales were used: 17-item version Hamilton Depression Rating Scale, Hamilton Anxiety Rating scale (HAM-A), Sheehan disability scale, the Child Trauma Questionnaire. The following biomarkers were investigated: lipid profile, including total cholesterol, high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol, triglycerides the Castelli's Risk indexes I and II; and cytokines, including interleukins (IL)-1β, IL-6, IL-10, IL-12, soluble tumor necrosis factor receptor 1 (sTNF-R1).
Results: Depressed female smokers showed a number of significant positive correlations: emotional neglect and sTNF-R1 ($p = 0.02$); waist circumference and sTNF-R1 ($p = 0.001$); body mass index and sTNF-R1 ($p < 0.01$); HAM-A and sTNF-R1 ($p = 0.03$); IL-1β and sTNF-R1 ($p < 0.01$); IL-10 and sTNF-R1 ($p = 0.001$); IL-12 and sTNF-R1 ($p < 0.01$); Castelli index I and sTNF-R1 ($p < 0.01$); Castelli index II and sTNF-R1 ($p < 0.01$); and a significantly negative correlation between HDLc and sTNF-R1 ($p = 0.014$).
Conclusion: This study suggests that depressed female smokers who experienced more childhood trauma and had more anxiety symptoms are associated with the activation of inflammatory processes and alterations in components of lipid profile.

1. Introduction

Unipolar and bipolar depression, as well as tobacco use disorder (TUD) have a significant global burden arising from heightened levels of chronicity, progressive disability and premature death. These disorders represent the leading causes of disability-adjusted life years (GBD 2015 Tobacco Collaborators et al., 2017; Murray et al., 2012; Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2015). The most common tobacco-related diseases are cardiovascular illnesses, chronic obstructive pulmonary disease and cancer (Ezzati & Lopez, 2003). Neoplasia, cardiovascular and respiratory diseases also affect bipolar disorder (BD) patients (Kupfer, 2005; Leboyer et al., 2012; McIntyre

et al., 2006). TUD associates with a wide array of medical conditions as a consequence of chronic inflammatory process (Yanbaeva, Dentener, Creutzberg, Wesseling, & Wouters, 2007).

Despite the raised awareness of tobacco–related diseases, rates of tobacco use are increasing in young females (Mamudu, Hammond, & Glantz, 2008). There is a relationship between smoking and depression, which may be of particular relevence in women, given that women have higher rates of depression and anxiety (Roehr, 2013). Women who quit smoking exhibit similar levels of depressive symptomatology as current smokers (Pomerleau, Zucker, & Stewart, 2003). TUD is a vulnerability factor for the development of severe depressive and anxiety symptoms (Jamal, Willem Van der Does, Cuijpers, & Penninx, 2012).

Furthermore, a history of mood disorders increases the risk of early onset cigarette smoking, as well as to progression from daily smoking to nicotine dependence (Breslau, Novak, & Kessler, 2004). Childhood abuse may affect risks of diabetes and cardiovascular disease later in life (Bertone-Johnson, Whitcomb, Missmer, Karlson, & Rich-Edwards, 2012).

TUD is highly comorbid with mood disorders, including (BD) and major depressive disorder (MDD). In the National Comorbidity Survey nearly 61.3% of people with a lifetime history of panic disorder and 68.4% with generalized anxiety disorders were current or past smokers, whilst only 39% of smokers showed no evidence of a psychiatric disorder. In major depressive disorder, TUD prevalence ranges from 40% to 64% across studies. Nicotine-dependent smokers are twice as likely as non-smokers to have a history of depression (Lasser et al., 2016; Ziedonis et al., 2008). Such studies indicate an intimate interaction of TUD and mood dysregulation.

This common co-occurrence of TUD and mood disorders has generated a number of theoretical explanations, including: cigarette smoking has anti-depressant effects, being a form of self-medication; TUD, BD and MDD share common environmental or genetic risk factors; BD and MDD are a consequence of brain dysfunction, which is worsened by TUD (Dome, Lazary, Kalapos, & Rihmer, 2010).

Both bipolar depression and MDD show evidence of heightened levels of pro-inflammatory and anti-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), soluble tumor necrosis factor receptor 1(sTNF-R1), interleukin -1β (IL-1β); IL-6, IL-8, IL-10, and IL-1 receptor antagonist (IL1RA), as well as acute phase proteins, such as C-reactive protein (CRP)(Barbosa et al., 2012; Brietzke et al., 2009; Doganavsargil-Baysal et al., 2013; Dowlati et al., 2010; Hope et al., 2015; Modabbernia, Taslimi, Brietzke, & Ashrafi, 2013; Munkholm, Bräuner, Kessing, & Vinberg, 2013; Myint et al., 2007; Young, Bruno, & Pomara, 2014). The levels of hs-CRP, TNF-α, sTNF-R1 and sTNF-R2 are also elevated in current smokers with cardiovascular disease and chronic obstructive pulmonary disease (Asthana et al., 2010).

Mood disorders, when coupled to TUD, show higher levels of pro-inflammatory cytokines, versus non-depressed smokers, including TNF-α, IL-6, and CRP (Nunes et al., 2012). The shared activated immune-inflammatory and oxidative and nitrosative stress pathways by which TUD may increase the risk for development of depressive disorders are, in part, mediated by increased levels of pro-inflammatory cytokines, diverse neurotransmitter systems, hypothalamic–pituitary–adrenal (HPA) axis activation, and microglial activation, as well as increased levels of endogenous oxidative stress and decreased levels of endogenous antioxidants (Nunes et al., 2013).

The present study evaluated the clinical and biomarker differences between females with mood disorders, either bipolar depression or MDD, when either comorbid, or not, with TUD.

2. Method

This study included non-depressed female and never-smokers ($n = 28$), non-depressed smokers female ($n = 24$), depressed never-smokers female ($n = 38$), and depressed smokers female ($n = 69$). Female smokers were outpatients recruited from the Cigarette Smoking Cessation Service Center, State University of Londrina (UEL). Depressed female were patients with BD or MDD, who were recruited from the outpatients Psychiatric Ambulatory Clinic (UEL). Control participants were regarded as non-depressed and never-smokers if they reported never having smoked a cigarette or have smoked < 100 cigarettes in their lifetime, coupled to no previous experience of a mood disorder. Controls were recruited from the staff at the same institution.

All participants were women aged 18–65 years. Exclusion criteria were: a) another medical condition or medication-induced BD and MDD; b) participants with a diagnosis of mental retardation, schizophrenia, psycho-organic syndromes or any condition that would compromise the understanding of the study terms and c) pregnancy. All

participants gave written informed consent to participate in the study after the approval of this research by the local Ethics Research Committee (number CAAE 34935814.2.0000.5231).

All participants completed a questionnaire, which comprised socio-demographic data (education, occupation, marital status years of education), and clinical data (hospitalizations, ability to work, smoking status, suicidal ideation and suicide attempts, as well as number of lifetime depressions).

Trained psychiatrists carried out the clinical assessments. Diagnoses were based on the Structured Clinical Interview for DSM-IV, Axis I (SCID-I), clinical version, translated and validated for the Portuguese language (Del-Ben et al., 2001) and on the 10th edition of the International Classification of Diseases (ICD-10) (World Health Organization., 1993).

Anxiety severity was assessed through Hamilton Anxiety Rating Scale (HAM-A) (HAMILTON, 1959).

Severity of depression was assessed through 17-item Hamilton Depression Rating Scale (HDRS$_{17}$) (HAMILTON, 1960). HDRS$_{17}$ was translated and adapted for the Brazilian population (Moreno & Moreno, 1998).

Quality of life was evaluated using the World Health Organization Quality of Life Instrument, abbreviated version (WHOQOL-BREF), comprised by 26 items, measuring the following broad domains: physical health, psychological health, social relationships and environment. This instrument was translated and adapted to Portuguese (Fleck et al., 2000).

The Childhood Trauma Questionnaire (CTQ) is a self-administered instrument used to document a history of childhood maltreatment in 5 domains: sexual abuse, physical abuse, emotional abuse, emotional neglect and physical neglect (Bernstein et al., 2003). The 28 item-version of CTQ was validated in the Portuguese language (Grassi-Oliveira, Stein, & Pezzi, 2006).

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein (LDL-c) and triglycerides levels were determined by an automated method, namely the Dimension® RXL (Siemens Healthcare Diagnostics Inc., Newark, DE, USA). HDL-c levels were measured directly, without the necessity of sample pretreatment or specialized centrifugation steps. LDL-c was calculated by Friedewald's equation. Serum triglycerides were measured using an enzymatic procedure employing combinations of enzymes. We computed the Castelli risk index1 [TC/HDL-c] and Castelli risk index 2 [LDL-c/HDL-c].

The luminex kit was utilized to measure the cytokines, IL-1β, IL-1RA, IL-6, IL10, IL-12, and sTNF-R1.

Statistical analyses were performed to examine the relationship between socio-demographic, clinical and laboratory measurements. ANOVA was used for quantitative comparisons among groups (mood disorder smokers; mood disorder never-smokers; non-mood disorder smokers; non-mood disorder, never-smokers), followed by the Tukey test when the assumptions were attended (homogeneity of variances and normality of the residuals). If these criteria were not met, the Kruskal-Wallis test was used, followed by a post hoc test.

For the qualitative variables, the Chi-square test or Fisher exact test was used, followed by the z-test, to compare the percentages among the groups. The statistical significance level used was 0.05 and when the *p*-value is < 0.05, the means (for the quantitative variables) or the percentages (for the qualitative variables) are followed by letters. The same letters for the same variable indicate that there are no differences between the means or percentages among the groups and different letters for the same variable indicate that there are differences between the means or the percentages among the groups.

Following these univariate comparisons Pearson correlation coefficients were utilized to compare some pairs of clinical and physiological data.

All the analyses were performed in software R (R foundation, 2018).