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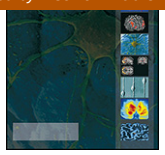

Oxidative stress and inflammatory markers are associated with depression and nicotine dependence☆

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HIGHLIGHTS

- Oxidative stress markers are associated with both depression and smoking.
- Increased nitric oxide and fibrinogen levels are seen in smokers and depression.
- There is a correlation between depressed smokers and lipid hydroperoxides.
- Depressed smokers have an elevated disability for work.
- Depressed smokers have a higher severity of depression and more suicide attempts.

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ABSTRACT

To determine if oxidative stress and inflammation are linked with major depressive disorder, nicotine dependence and both disorders combined. This study comprised 150 smokers and 191 never smokers. The instruments were: a socio-demographic questionnaire, diagnoses of mood disorder and nicotine dependence according to DSM-IV, (SCID-IV), and the Alcohol, Smoking and Substance Involvement Screening Test. Laboratory assessments included: nitric oxide metabolites (NOx), lipid hydroperoxides, malondialdehyde (MDA), total reactive antioxidant potential (TRAP), advanced oxidation protein products (AOPP), fibrinogen concentrations, homocysteine, erythrocytes sedimentation rate (ESR) and high-sensitivity C-reactive protein (hs-CRP) were assayed from blood specimens. Statistically significant differences were found among depressed smokers who had more severe depressive symptoms, a higher risk of alcohol consumption, more suicide attempts, and more disability for work than non-depressed never smokers. Depressed smokers had significantly higher levels of NOx, fibrinogen, hs-CRP, AOPP, ESR and lower levels of TRAP compared to non-depressed never smokers. Depressed smokers had significant levels of oxidative stress and inflammatory biomarkers after adjusting for gender, age, years of education, disability for work, and laboratory measures. The levels of NOx, lipid hydroperoxides, AOPP, and fibrinogen were substantially higher, whereas levels of TRAP were lower in depressed smokers compared to non-depressed never smokers. (1) Depressed smokers exhibited altered concentrations of NOx, lipid hydroperoxides, AOPP, TRAP, and fibrinogen. (2) Depressed smokers were more unable to work, showed more severe depressive symptoms and attempted suicide more frequently.

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1. Introduction

Tobacco use is a risk factor for disability and morbidity, as well as the most preventable cause of death in the world [32]. Smokers more often presented with impaired work/domestic functionality, more frequent hospitalization, more depressive disorders, more sedative use and a family history of mental disorders, as well as scoring lower on the quality of life scale compared with never smokers [6]. Smoking with nicotine dependence increases the risk of developing major depressive disorders [25], contributes to more severe depressive symptoms [3,14] and is associated with suicidal behavior [4,20].

Major depressive disorder is accompanied by an increase in oxidative stress and a decrease in antioxidant status, which damages neurons and has an important role in the pathophysiology of depressive disorders [2,10,17,19,22]. There is also data linking oxidative stress and nicotine dependence [28]. Oxidative and nitrosative stress and inflammation induced damage to fatty acids, proteins, DNA, mitochondria and consequent autoimmune reactions, which link to neuroprogression and degenerative processes that occur in depressive disorders [2,19]. Nitric oxide plasma concentration is associated with cognitive impairment in patients with recurrent depressive disorders [29]. These alterations may lead brain damage, which may be a pathway to neurodegenerative diseases [13], as well as neuroprogression of mood disorders [2,19].

The purpose of this study was to elucidate the involvement of oxidative and nitrosative stress and inflammatory markers, including nitric oxide metabolites (NOx), lipid hydroperoxides, malondialdehyde (MDA), advanced oxidation protein products (AOPP), total reactive antioxidant potential (TRAP) and inflammatory biomarkers (high-sensitivity C-reactive protein (hs-CRP), fibrinogen, homocysteine, erythrocytes sedimentation rate (ESR)) in depressed and non-depressed smokers compared to depressed and non-depressed never smokers. We also hypothesized that depressive smokers would have co-occurring disorders such as more risk of alcohol use, more suicide attempts, more physical diseases, more severe symptoms, as well as more disability for work than non-depressed never smokers.

2. Materials and methods

2.1. Study population

Smokers ($n = 150$) were recruited from outpatients at the Centre of Approach and Treatment for Smokers, at Londrina State University (UEL), Paraná, Brazil and never smokers ($n = 191$) were recruited from staff of UEL. The sample size calculation of was based on smokers and never smokers with and without depression. The study sample size calculation showed that a sample of 34 never smokers and 27 smokers (total $n = 61$) would be able to detect a 59% prevalence of depressive disorders among smokers compared to 17% depressive disorders among non-smokers (odds ratio = 7.03) with a confidence level of 0.95 and 95% power. It was assumed that the ratio of control to case was 1.27. However we are able to recruit 191 never smokers and 150 smokers and that sample size would be adequately powered to detect population level prevalence of depressive disorders among smokers and never smokers as reported in the literature [6,7].

Smokers and never smokers were men and women aged 18–60 and all ethnicities were accepted for this study. The study was conducted from March 2011 to July 2012.

Exclusion criteria were presence of medical comorbidities including chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, HIV infection, neurodegenerative and neuroinflammatory disorders, such as Alzheimer's, Huntington's and Parkinson's disorder, multiple sclerosis and stroke, conditions such as hemodialysis, use of interferon. All these conditions are known to share peripheral inflammation and cell-mediated immune activation [17]. All study participants needed to have normal blood values on the following laboratory tests: hemogram, aspartate transaminase (AST), alanine transaminase (ALT), urea, and creatinine.

All subjects had given written informed consent to participate in the study after the approval of this research by the Ethics Research Committee at Londrina State University (UEL), number 250/2010.

2.2. Instruments

2.2.1. Questionnaire

A self-reported questionnaire was used to gather information on socio-demographic, clinical characteristics and smoking status.

2.2.2. Major depressive disorder and nicotine dependence

The diagnoses of major depressive disorder and nicotine dependence were made at interview by a trained clinician using DSM-IV, criteria translated and validated into Portuguese [8].

2.2.3. Hamilton Depression Rating Scale

A translated and validated version of the Hamilton Depression Rating Scale, adapted to the Brazilian cultural context and Portuguese language [21] was used to measure the severity of depression in study participants who had been diagnosed with major depressive disorder.

2.2.4. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

The World Health Organization (WHO) developed Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) is a questionnaire to screen for levels of risk for alcohol, smoking and substance use in adults. ASSIST scores were calculated for all participants. A risk score for alcohol was calculated as low risk (score 0–3), moderate risk (score 4–26) or high risk (score $\geq$27) [31].

2.3. Laboratory assessments

Peripheral blood samples were collected from all participants after 12–14 h overnight fasting. Lipid hydroperoxides were measured by the ferrous oxidation of xylenol assay using an adaptation of the technique described by Jiang [16]. The levels of nitric oxide metabolites (NOx) were assessed by measuring the plasma concentration of nitrite and nitrate, using an adaptation of the technique described by Navarro-Gonzálvez et al. [23]. TRAP was measured by chemiluminescence in an adaptation of the method described by Repetto et al. [27]. The quantification of advanced oxidation protein products (AOPP) in plasma used the method described by Witko-Sarsat et al. [30]. Malondialdehyde (MDA) is a secondary product of lipid peroxidation and was determined using the method described by Jentzch et al. [15].

We measured the serum concentration of hs-CRP by immunonephelometry system on a BNII analyzer (Siemens® System BNTMII, Deerfield, IL, USA). ESR was performed by an automatic analyzer for erythrocyte sedimentation rate determination (MicroTest1X – Sire Analytical Systems, Udine, Italy). The quantitative determination of fibrinogen in plasma was based on the Clauss method. This method measures the rate of fibrinogen to fibrin conversion in the presence of excess thrombin. This method was performed by a coagulation analyser (Destiny Plus – Trinity Biotech GmbH, Lemgo, Germany). The determination of serum homocysteine was performed on an ARCHITECT i System (Abbot, Wiesbaden, Germany).

Table 1
Demographic and clinical characteristics by smoking and depressive disorder.

Characteristics	Never-smoker				Smoker				*p*-Value[a]
	Non-depressed ($n=123$)		Depressed ($n=68$)		Non-depressed ($n=78$)		Depressed ($n=72$)		
	n	%	*n*	%	*n*	%	*n*	%	
Gender									0.008
Male	47	(38.2)	14	(20.6)*	35	(44.9)	20	(27.8)	
Female	76	(61.8)	54	(79.4)*	43	(55.1)	52	(72.2)	
Age									0.079
18–29	6	(4.9)	1	(1.5)	4	(5.1)	6	(8.3)	
30–39	18	(14.6)	8	(11.8)	8	(10.3)	12	(16.7)	
40–49	63	(51.2)	38	(55.9)	29	(37.2)	25	(34.7)*	
50–60	36	(29.2)	21	(30.9)	37	(47.4)**	29	(40.3)	
Ethnicity									0.524
Caucasian	84	(68.3)	48	(70.6)	53	(67.9)	48	(66.7)	
African	14	(11.4)	5	(7.4)	8	(10.3)	9	(12.5)	
Asian	9	(7.3)	3	(4.4)	4	(5.1)	0	(.0)*	
Mixed	16	(13.0)	12	(17.6)	13	(16.7)	15	(20.8)	
Marital status									0.289
Stable relationship	85	(69.1)	48	(70.6)	52	(66.7)	40	(55.6)	
Years of education									0.000
≤12 years	28	(22.8)	9	(13.2)	58	(74.4)**	51	(70.8)**	
≥13 years	94	(76.4)	55	(80.9)	19	(24.4)**	18	(25.0)**	
Disability for work									0.000
Yes	2	(1.6)	1	(1.5)	14	(17.9)**	19	(26.4)**	
Suicide attempt									
Yes	0	(.0)	2	(2.9)	2	(2.6)	22	(30.6)**	0.000
Hamilton scale (mean, SD)									
Yes	1.6	(2.3)	6.9	(7.9)	4.5	(4.6)	14.4	(9.4)**	0.000
Alcohol ASSIST									
Yes	1	(.8)	1	(1.5)	8	(10.3)**	16	(22.2)**	0.000

[a] The *p*-value tests based on Pearson Chi-square test. The Hamilton scale based Kruskal–Wallis test, other characteristics it is based on the Pearson Chi-square test.
* $p=0.05$.
** $p=0.01$.

2.4. Statistical analyses

Analyses were performed examining the relationship between the non-depressed never-smoker with depressed smokers, non-depressed smokers and depressed never smokers. Comparisons were made between these for socio-demographic, clinical and laboratory measurements, using appropriate parametric tests where data were normally distributed and non-parametric statistical tests for categorical or non-normal data. All tests were 2-tailed and a *p*-value of 0.05 was used for statistical significance.

Univariate comparisons were initially conducted and then variables that were statistically significant were included in the multivariate analyses. A generalized multinomial regression analysis was carried out using non-depressed never-smoker, depressed never-smoker, non-depressed smoker and depressed smoker categories as the dependent variable. The multinomial regression analysis was used to estimate the odds that depressed never-smokers, non-depressed smokers or depressed smokers, compared with non-depressed never-smokers, was associated with each of the independent variables. All analyses were performed using SPSS (Version 20).

3. Results

In examining socio-demographic and clinical variables, smoking and depressive status did not differ with respect to marital status, age and ethnicity. The depressed and non-depressed smokers were significantly different in having fewer years of education and more disability for work compared to non-depressed never smokers ($p<0.01$). Depressed smokers had significantly more disability for work than non-depressed never smokers ($p<0.01$). The mean age for all groups was 46.25 years (Table 1).

Depressed smokers showed statistically significant differences in consuming more alcohol, requiring more frequent hospitalization, attempting suicide more frequently, and being more unable to work than non-depressed never smokers. The depressed smokers also exhibited significant differences in severity of depression (higher Hamilton scores) compared with depressed never smokers (Table 1).

Depressed smokers had significantly higher levels of oxidative stress (NOx, AOPP) and lower levels of antioxidants (TRAP), higher levels of inflammatory biomarkers (fibrinogen, hs-CRP, ESR) compared to non-depressed never smokers However, smokers from all groups did not differ with respect to levels of homocysteine, lipid hydroperoxides and MDA (Table 2).

These results did not change when we analyzed these variables using multinomial regression analysis after adjusting for gender, age, years of education, disability for work, and laboratory measures. We found the levels of NOx, AOPP (OR = 1.02, 95% CI = 1.01–1.03), and fibrinogen were substantially higher, and levels of TRAP were lower (OR = 0.99, 95% CI = 0.99–1) in depressed smokers compared to non-depressed never smokers. However, the association between hs-CRP and ESR in depressed smokers was no longer significant after the multinomial regression analysis. On the other hand, we found significant differences in levels of lipid hydroperoxides (OR = 3.14, 95% CI = 1.25–7.88) (Table 3).

Using multinomial regression analysis, depressed never smokers comprised more women (odds ratio was 4.06, 95% CI = 1.58–10.43) compared to non-depressed never smokers. Depressed smokers were more unable to work (OR = 7.85, 95% CI = 1.29–47.90) compared to non-depressed never smokers.

4. Discussion

The current study demonstrated that depressed smokers had significantly higher levels of oxidative stress such as raised NOx (products of nitrates and nitrites), lipid hydroperoxides (a biomarker of oxidative damage to lipids), AOPP (a biomarker

Table 2
Comparison of laboratory measurements of oxidative stress and inflammatory biomarkers by smoking status and/or depressive disorder.

Laboratory measures	Never-smoker				Smoker				*p*-Value[a]
	Non-depressed		Depressed		Non-depressed		Depressed		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
CRP	2.8	(4.1)	2.5	(3.4)	4.1	(4.7)**	4.1	(4.7)**	0.000
NOx	3.3	(1.8)	3.3	(2.1)	5.3	(2.7)**	4.5	(2.1)**	0.000
Lipid hydroperoxides	0.9	(.4)	0.9	(.4)	1.0	(.4)	1.1	(.6)*	0.125
AOPP	98.5	(38.6)	103.5	(41.8)	109.9	(46.9)**	117.3	(48.0)**	0.018
TRAP	838.3	(131.7)	830.7	(135.3)	836.0	(142.5)	780.1	(126.8)**	0.020
MDA	16.0	(5.4)	14.8	(5.4)	16.0	(5.4)	16.4	(7.1)	0.501
Fibrinogen	327.9	(66.2)	323.4	(62.1)	368.1	(73.8)**	365.6	(67.9)**	0.000
ERS	12.3	(10.8)	11.5	(9.1)	14.6	(10.5)	17.8	(14.3)*	0.015

[a] The *p*-value for all the laboratory measurements except TRAP is based on the independent samples Kruskal–Wallis test and for TRAP it is based on the oneway ANOVA.
* Significance at the 0.05 level.
** Significance at the 0.01 level and the comparison is between the non-depressed never-smokers and the other three groups based on the Mann–Whitney *U* test for all variables except TRAP and for TRAP it is based on the independent sample *t*-test.

of oxidative damage to proteins) and lower levels of TRAP (a biomarker of anti-oxidants) than non-depressed never smokers. In depressed smokers we also found differences in inflammatory biomarkers such as fibrinogen compared to non-depressed never smokers. Furthermore, non-depressed and depressed smokers had significantly higher levels of NOx and fibrinogen compared to non-depressed never smokers. Our results were consistent with previous studies which have examined markers of oxidative stress disturbances in patients with depression, but which did not consider comorbid nicotine dependence [10,29]. Our study included depressed smokers with nicotine dependence.

This study provides evidence for an association between depressed smokers and higher levels of AOPP, a measure of oxidation damage to proteins [1]. AOPP correspond to highly oxidized proteins and specifically to albumin and might be formed during oxidative stress by reaction of plasma proteins with chlorinated oxidants. Thus, AOPP have been considered as a novel marker of oxidant-mediated protein damage [1].

Patients with both major depression and nicotine dependence also had higher levels of lipid hydroperoxides, a marker of oxidative damage. Consistent with previous research that found higher levels of serum F2a-isoprostanes (8-iso-PGF2a), we found high levels of lipid hydroperoxides, a biomarker of oxidative damage to lipids, in depressed compared to non-depressed individuals [33]. Furthermore, depressive smokers had significantly lower concentrations of TRAP, a measure of global antioxidant defenses. Cigarette smoking and depression are significant factors in alterations of the oxidant and antioxidant balance in blood, resulting in potent oxidative stress and in these conditions a lipoperoxidation process can occur [5,19].

In our study, fibrinogen concentrations were higher in smokers with and without depression compared to non-depressed never smokers. These findings are in accordance with other research that has found strong associations between fibrinogen, persistent depressive symptoms and smoking [12]. Fibrinogens and hs-CRP are inflammatory biomarkers. Thus, cigarette smoking and depressive disorders may increase the levels of inflammatory biomarkers and the production of oxidants, and may decrease the levels of antioxidants. An increase in inflammation and oxidative stress is documented in mood disorders [2,19]. There is also data linking oxidative stress and inflammation in cigarette smoking and lung disease [28].

Higher levels of CRP were consistently associated with depressive disorder, and remained significant after controlling for gender, age, smoking status, physical activity weight, as well as medication use and medical conditions potentially influencing inflammation levels [9,18,25]. Furthermore, in univariate analyses, there were higher levels of CRP in smokers with and without depression than non-depressed never smokers. However, in multinomial analysis our data did not suggest that the highest levels of CRP were a consequence of smoking or depressive disorder.

Our study found an association between higher levels of NOx and smokers with and without depression compared with non-depressed never smokers. Higher concentration of plasma NOx in patients with recurrent depressive disorder was associated with the severity of depressive symptom and cognitive impairment,

Table 3
Multinomial regression analysis of variables associated with smoking and/or depression.

Independent variables	Depressed never-smoker versus non-depressed never-smokers			Non-depressed smoker versus non-depressed never-smokers			Depressed smoker versus non-depressed never-smokers		
	OR[b]	95% CI	*p*-Value	OR[b]	95% CI	*p*-Value	OR[b]	95% CI	*p*-Value
Female[a]	4.06	(1.58–10.43)	0.00**	0.84	(0.34–2.08)	0.70	1.48	(0.55–3.98)	0.44
Age	1.02	(0.98–1.07)	0.29	1.02	(0.98–1.07)	0.30	0.99	(0.95–1.04)	0.74
Years of education	1.03	(0.96–1.12)	0.40	0.78	(0.72–0.86)	0.00**	0.82	(0.75–0.90)	0.00**
Disability for work,[a] yes	0.60	(0.04–8.32)	0.70	5.17	(0.86–30.99)	0.07	7.85	(1.29–47.9)	0.03*
CRP	0.98	(0.88–1.09)	0.72	0.94	(0.85–1.04)	0.25	0.93	(0.83–1.03)	0.16
NOx	1.03	(0.85–1.25)	0.75	1.45	(1.21–1.75)	0.00**	1.28	(1.05–1.57)	0.02*
Lipid hydroperoxides	1.56	(0.65–3.71)	0.32	1.41	(0.56–3.52)	0.47	3.14	(1.25–7.88)	0.01*
AOPP	1.01	(1.00–1.02)	0.15	1.01	(1.00–1.02)	0.10	1.02	(1.01–1.03)	0.00**
TRAP	1.00	(1.00–1.00)	0.56	1.00	(0.99–1.00)	0.07	0.99	(0.99–1.00)	0.00**
Fibrinogen	1.00	(0.99–1.01)	0.63	1.01	(1.01–1.02)	0.00**	1.01	(1.01–1.02)	0.00**
ERS	0.96	(0.92–1.01)	0.11	0.96	(0.92–1.00)	0.07	0.97	(0.93–1.01)	0.18

[a] Reference categories: gender, male; disability for work, no.
[b] Odds ratios (OR) mutually adjusted for each of the presented variables.
* $p = 0.05$.
** $p = 0.01$.

suggesting that an overproduction of nitric oxide via inducible nitric oxide synthase, inducible nitric oxide synthase (iNOS), which results in oxidative stress and cell damage [29]. Increased production of NO and peroxynitrite may cause nitration and nitrosylation of proteins that appears related to the pathogenesis of depression [22]. Induction of nitric oxide leads to an activation of nuclear factor kappa B (NF-κB), which is relevant to the development of depressive disorders [26].

Depressive smokers were more unable to work, showed more severe depressive symptoms and attempted suicide more frequently compared with non-depressed never smokers. Our data are consistent with previous reports that have shown that current smoking is associated with subsequent suicidal behavior [4] and more disability for work and more hospitalization [7,24].

The results of this study should be interpreted with regard to its strengths and limitations. The present study design was a cross-sectional study, which can only examine an exposure at a particular time, but cannot determine causal relationships [11]. In our study, the never smokers were highly educated; this could generally lead to healthy behavior patterns.

Despite of some limitations, our findings provide evidence of a link between depressed smokers and altered oxidative stress and inflammatory marker. In addition, our data suggest that depressed smokers were more unable to work, showed more severe depressive symptoms and attempted suicide more frequently.

5. Conclusion

Our results corroborate the inflammatory, oxidative and nitrosative stress theory of depression, and suggest that inflammatory, oxidative and nitrosative stress could be worsened by concomitant nicotine dependences. Depressed smokers exhibited altered concentrations of NOx, lipid hydroperoxides, AOPP, TRAP, and fibrinogen. Depressive smokers were more unable to work, showed more severe depressive symptoms and attempted suicide more frequently.

These findings need further studies to better understand the role of shared inflammatory, oxidative and nitrosative stress pathways in depressive disorders and nicotine dependence, which impacts on the course and severity of both diseases. The translational implications of these findings include the opportunity to identify subgroups of major depressive disorder with comorbidity with nicotine dependence, to potentially protect them from the effects of oxidants by applying new therapies.

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