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A Case Control Study of Oxidative Stress in A Sample of Patients with Major Depressive Disorder

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Abstract

Background: *The relationship between depression and oxidative stress is considered bidirectional as both conditions can affect each other. The presence of depression increases the magnitude of oxidative stress state and therefore the morbidities associated with this state. The aim of this work was to prove the importance of early detection and management of mild to moderate depression (MMD) and to highlight the importance of family physician's role in depression screening.*

Methods: *This case-control study was carried out on 45 patients aged from 18 to 45 years old, both sexes, diagnosed with depression according to diagnostic and statistical manual of mental disorders V criteria (Group 1) and 45 healthy control subjects matched for age and sex without history of psychiatric disorders or chronic medical disease (group 2). Oxidized low-density lipoprotein (LDL) and super oxide dismutase (SODs) were measured in all patients. Psychometric measurements were done through Beck Depression Inventory (BDI-II) 1996 (appendix 1), symptom Checklist-90-R (SCL-90-R) Arabic version (SCL90), State-Trait Anxiety Inventory (STAI) Arabic version and general health questionnaire (GHQ-28).*

Results: *LDL was significantly higher in Group 1than Group 2. SODs were significantly lower in Group 1 than Group 2. There was a negative correlation between Oxidized LDL and SCL- obsessive-compulsive disorder (OCD) and between SODs and (SCL hostility and SCL psychoticism). There was a positive correlation between SODs and (SCL somatization and paranoia). STAI and SCL score interpretation were significantly higher in negative group than positive group (P<0.05).*

Conclusions:

The severity of oxidative stress state was not correlated to severity of depression. This study's results go in concomitance with previous studies' results regarding the proven association between MMD and oxidative stress state, lack of association between degree of severity of both conditions, and the confirmed association of anxiety trait to oxidative stress state.

Key words: *Oxidative Stress, Depression, Super Oxide Dismutase, Low Density Lipoprotein.*

Introduction

Major depressive disorder (MDD) affects millions of individuals, an estimated 3.8% of people suffer from depression, including 5.7% of individuals over 60 and 5% of adults (4% of males and 6% of women). Women are around 50% more likely than men to experience depression. Moreover 10% of expectant mothers and recent mothers experience depression globally [1].

Oxidative stress results from lack of cellular equilibrium between pro-oxidant and antioxidant species. Oxidative stress is characterized by an excessive rise in reactive oxygen species (ROS), which is supported by a deficient antioxidant defence or a breakdown of the cells' buffering system to maintain the redox equilibrium [2].

Depression is highly comorbid with many age-associated diseases such as diabetes mellitus, immune-

inflammatory dysregulation and cardiovascular diseases. Oxidative stress also plays a fundamental role in the pathogenesis of neurodegenerative/neuropsychiatric disorders including MDD. There is evidence of the association between MDD and changes in molecular mechanisms [3].
The relationship between depression and oxidative stress is considered bidirectional as both conditions can affect each other. In other words, the presence of depression increases the magnitude of oxidative stress state and therefore the morbidities associated with this state [4].
Despite the fact that mild to moderate depression (MMD) is underdiagnosed, research in the past decade has focused on the link between severe depression and oxidative stress [5].
It was hypothesized that MMD is associated with oxidative stress state that can affect different health systems [6]. Therefore, screening and early detection of cases with MMD could prevent the hazardous effect of depression and its subsequent ramifications on the health. Moreover, treatment of depression in its early phase could be hopeful with lower costs as research has validated 5ognitive behavioural therapy (CBT) as a useful therapy for MMD patients. Also, primary prevention of MMD could decrease the health burden especially in low-income countries [7].
The aim of this work was to prove the importance of early detection and management of MMD, highlighting the importance of family physician's role in depression screening.

Patient and method:

This case-control study was carried out on 45 patients aged from 18 to 45 years old, both sexes, body mass index (BMI) 18-25Kg/m2 diagnosed with depression according to diagnostic and statistical manual of mental disorders (DSM) V criteria and 45 healthy individuals as control. The study was done after approval from the Ethical Committee Cairo University Hospitals, Cairo, Egypt. An informed written consent was obtained from the patients.
Exclusion criteria were patients receiving antipsychotic treatment, antidepressants as well as patients on mood stabilizers, patients on therapy for hypertension, diabetes mellitus, hypothyroidism, dyslipidemia, obese and overweight individuals as defined by BMI more than 25, patients who have acute illness, patients who have autoimmune disease, or receiving corticosteroid therapy, smoking, BMI justification: in order to avoid confounding oxidative stress state found in obesity and smoking increases oxidative stress state.
Patients were divided into two equal groups: Group 1: diagnosed as depression by the researcher according to DSM V criteria and Group 2: Healthy control subjects matched for age and sex without history of psychiatric disorders or chronic medical disease.
All patients were subjected to complete history taking, clinical examination, laboratory investigations [HBA1C, lipid profile, oxidized low-density lipoprotein (LDL) and super oxide dismutase (SODs)] and psychometric measurements [A semi-structured interview guide was conducted to both groups for making diagnoses and beck Depression Inventory (BDI-II) 1996 (appendix 1)].

The Beck Depression Inventory (BDI-II) 1996 (appendix 1):

The BDI-II contains 21 questions, each answer being scored on a scale value of 0 to 3. It is the most commonly used instrument that measures depressive symptoms with scores as follows: [0 – 13: minimal depression, 14 – 19: mild depression, 20 – 28: moderate depression and 29 – 63: severe depression]. The BDI has good reliability and validity.12 The test-retest reliability of the BDI-II ranged from 0.73 to 0.92, which means that the scores are consistent over time. The internal consistency of the BDI-II was 0.9, which means that the items on the questionnaire relate to each other and measure the same construct [8].

The Symptom Checklist-90-R (SCL-90-R) Arabic version (SCL90) (appendix 2):

Is a brief self-report questionnaire that consists of 90 items and takes 12–15 minutes to administer, yielding nine scores along primary symptom dimensions and three scores among global distress indices. The primary symptom dimensions that are assessed are somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. The SCL -90 Revised is an established instrument and has over 1,000 independent studies supporting is reliability and validity. The internal consistency coefficient rating ranged from 0.90 for Depression and 0.77 for Psychoticism. Test-retest reliability has been reported at 0.80 to 0.90 with a time interval of one week [9].

The State-Trait Anxiety Inventory (STAI) Arabic version (appendix 3) [10]:

The STAI consists of separate self-report scales for measuring two distinct anxiety concepts: state anxiety and

trait anxiety. State anxiety is conceptualized as a transitory emotional state or condition that is characterized by subjective, consciously perceived feelings of tension and apprehension and heightened autonomic nervous system activity. Participants completed the STAI, using a 4-point scale (1-2-3-4); participants answered 20 items assessing state (momentary, reactive) anxiety, and 20 items assessing trait (stable, dispositional) anxiety. Total scores were based on the sum of these values; the range of scores is 20-80, the higher score indicates greater anxiety. STAI showed relatively high degree of reliability and validity, responsiveness [11].

General health questionnaire (GHQ-28) (appendix 4) [12]:

It was initially developed as a first stage screening instrument for psychiatric illness in order to identify potential "cases" which could then be verified and the nature of which could be determined by using a second stage instrument as clinical interview schedule. It includes 4 factors labeled scale "A" somatic symptoms, scale "B" anxiety and insomnia, scale "C" social dysfunction and scale "D" severe depression. The total score of the GHQ 28 ranges from 0-28 with frequently used cut-off score 4/5 (a score within the range of 0-4 representing absence of psychopathology). The GHQ-28 was an internally consistent measure. Cronbach's α, split-half coefficients and test-retest reliability were 0.9, 0.89 and 0.58 respectively [13].

Oxidized low density lipoprotein:

Oxidation of LDL triggers the generation of a series of oxidation byproducts. They play important roles in the early development of atherosclerosis through the recruitment of monocyte-derived macrophages into the arterial wall, and by promoting the intracellular accumulation of choresteryl esters in these cells, resulting in the formation of foam cells. Oxidation of LDL triggers the generation of a series of oxidation byproducts [17].

By diluting the standard by small tubes first, then pipetting the volume of 50 µl from each tube to microplate well, each tube uses two wells, total ten wells. In the Microelisa sripplate, leaved a well empty as blank control. In sample wells, 40 µl Sample dilution buffer and 10 µl sample were added (dilution factor is 5). Samples were loaded onto the bottom without touching the well wall. Mixed well with gentle shaking. Incubated 30 min at 37℃ after sealed with Closure plate membrane. Diluted the concentrated washing buffer with distilled water (30 times for 96T and 20 times for 48T). Carefully peel off Closure plate membrane, aspirate, and refill with the wash solution. Discard the wash solution after resting for 30 seconds. Repeat the washing procedure 5 times. Add 50 µl HRP-Conjugate reagent to each well except the blank control well. Incubation as described in Step 3. Washing as described in Step 5. Add 50 µl Chromogen Solution A and 50 µl Chromogen Solution B to each well, mixed with gently shaking and incubate at 37℃ for 15 minutes. Add 50 µl stop solution to each well to terminate the reaction.

The color in the well changed from blue to yellow. Read absorbance O.D. at 450nm using a Microtiter Plate Reader. The OD value of the blank control well is set as zero. Assay was carried out within 15 minutes after adding stop solution. Assay range: 15 pg/ml-800 pg/ml.

Sensitivity: 3.8 pg/ml [14].

Super oxide dismutase:

Our Human Superoxide Dismutages, SOD ELISA Kit is to assay SOD levels. in Human serum, plasma, culture media or any biological fluid. By diluting the standard by small tubes first, then pipetting the volume of 50 µl from each tube to microplate well, each tube used two wells, total ten wells. In the Microelisa sripplate, leave a well empty as blank control. In sample wells, 40 µl Sample dilution buffer and 10 µl sample were added (dilution factor is 5). Samples were loaded onto the bottom without touching the well wall. Mixed well with gentle shaking. Incubate 30 min at 37℃ after sealed with Closure plate membrane. Dilute the concentrated washing buffer with distilled water (30 times for 96T and 20 times for 48T). Carefully peel off Closure plate membrane, aspirate, and refill with the wash solution. Discard the wash solution after resting for 30 seconds. Repeat the washing procedure 5 times. Add 50 µl HRP. Conjugate reagent to each well except the blank control well. Incubation as described in Step. Washing as described in Step 5. Add 50 µl Chromogen Solution A and 50 µl Chromogen. Solution B to each well, mix with gently shaking and incubate at 37℃ for 15 minutes. Termination: add 50 µl stop solution to each well to terminate the reaction. The color in the well changed from blue to yellow. Read absorbance O.D. at 450nm using a Microtiter Plate Reader. The OD value of the blank control well is set as zero. Assay was carried out within 15 minutes after adding stop solution.

Sample Size Calculation:

Sample size calculation was done using the comparison of oxidized LDL level between patients with depression

and normal volunteers. As reported in previous publication, the mean ± SD of oxidized LDL in depression group was 606.6 ± 440.9 U/L, while in healthy volunteers it was 207.4± 297.7 U/L. Accordingly, we calculated that the minimum proper sample size was 45 participants in each group to be able to detect a real difference of 399.2 U/L (one average SD) with 80% power at α = 0.05 level using Student's t test for independent samples. Sample size calculation was done using Stata® for Windows running machine (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC, USA).

Statistical Analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t-test. Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi-square or Fisher's exact test when appropriate. A two-tailed P value < 0.05 was considered statistically significant.

Results:

Age and sex were insignificantly different between both groups. Marital status (married) and educational level (high) were significantly lower in Group 1 Than Group 2 (P <0.05). Table 1

Table 1: Demographic data of the studied groups

		Group 1 (n=45)	Group 2 (n=45)	P
Age (years)		31.89 ± 6.91	34.47 ± 6.24	0.067
Sex	Male	7 (15.56%)	3 (6.67%)	0.314
	Female	38 (84.44%)	42 (93.33%)	
Marital status	Single	21(46.7%)	13 (28.9%)	0.024*
	Married	21(46.7%)	32 (71.1%)	
	Divorced	3 (6.7%)	0(0.0%)	
Educational level	Secondary	11(24.4%)	0(0%)	<0.001*
	High	34 (75.6%)	45(100%)	

Data are presented as mean ± SD or frequency (%). *Significant as P value ≤0.05.

Clinical data and psychometric measurements were explained in this table. Table 2

Table 2: Clinical data and psychometric measurements of the studied group 1

		N=45
BDI-II-degree score	Mild	15 (33.3%
	Moderate	30 (66.7%)
STAI-state	Moderate-severe	20 (44.4%)
	High anxiety	25 (55.6%)
STAI-Trait scale	Moderate-severe	23 (51.1%)
	High anxiety	22 (48.9%)
SCL score interpretation	Needs treatment	17 (37.8%)
	No	28 (62.2%)
BDI-II scores		24.644±3.632
Somatic GHQ		18.267±2.330
Anxiety GHQ		17.378±3.774
Social GHQ		16.800±2.857
Severe depression GHQ		5.489±3.894
Score		56.489±7.783
SCL somatization		49.200±5.798
SCL-OCD		29.889±11.058
SCL interpersonal sensitivity		37.222±11.985
SCL depression		56.289±5.303
SCL anxiety		47.71±8.041
SCL hostility		34.222±6.263
SCL phobia		31.844±0.638
SCL paranoia		29.422±1.305
SCL psychoticism		31.400±1.156

SCL- score	52.156±16.004

Data are presented as mean ± SD or frequency (%). *Significant as P value ≤0.0. BDI: Beck Depression Inventory, STAI: State-Trait Anxiety Inventory, SCL: Symptom Checklist, GHQ: General health questionnaire, OCD: Obsessive-compulsive disorder.

Oxidized LDL was significantly higher in Group 1than Group 2 (P <0.001). SODs was significantly lower in Group 1 than Group 2 (P <0.001). Table 3

Table 3: Oxidized LDL and SODs of the studied groups

	Group 1 (n=45)	Group 2 (n=45)	P
Oxidized LDL (U/L)	1100.02± 863.509	328.64±170.30	<0.001*
Negative	22 (48.9%)	45(100%)	<0.001*
Positive	23(51.1%)	0(0%)	
SODs (U/mL)	5.8±2.4	19.4±10.5	<0.001*
Negative	39 (86.67%)	8 (17.78%)	<0.001*
Positive	6 (13.04%)	37 (80.43%)	

Data are presented as mean ± SD or frequency (%). *Significant as P value ≤0.0. LDL: Low-density lipoprotein, SODs: Super oxide dismutase.

Sex (female) and marital status (married) were significantly higher in negative group than positive group (P<0.05). Educational level, BDI-II-degree score, STAI-state, STAI-Trait and SCL score interpretation were insignificantly different between negative and positive groups. Table 4

Table 4: Relation between Oxidized LDL and baseline parameters, BDI-II degree, STAI-state, STAI-Trait and SCL score interpretation of the studied groups

		Negative (n=67)	Positive (n=23)	P
Sex	Male	9 (13.43%)	8 (34.78%)	0.024*
	Female	58 (86.57%)	15 (65.22%)	
Educational level	Secondary	6 (8.96%)	5 (21.74%)	0.106
	High	61 (91.04%)	18 (78.26%)	
Marital status	Single	22 (32.84%)	12 (52.17%)	0.040*
	Married	44 (64.71%)	9 (37.5%)	
	Divorced	1 (1.49%)	2 (8.7%)	
		Negative (n=22)	Positive (n=23)	
BDI-II degree	Mild	7 (31.82%)	8 (34.78%)	0.833
	Moderate	15 (68.18%)	15 (65.22%)	
STAI-state	High anxiety	9 (40.91%)	11 (47.83%)	0.641
	Moderate-severe	13 (59.09%)	12 (52.17%)	
STAI-Trait	High anxiety	11 (50%)	12 (52.17%)	0.884
	moderate-severe	11 (50%)	11 (47.83%)	
SCL score interpretation	Needs treatment	7 (31.82%)	10 (43.48%)	0.420
	No	15 (68.18%)	13 (56.52%)	

Data are presented as frequency (%). *Significant as P value ≤0.0. LDL: Low-density lipoprotein, BDI: Beck Depression Inventory, STAI: State-Trait Anxiety Inventory, SCL: Symptom Checklist.

There was a negative correlation between Oxidized LDL and SCL-OCD and between SODs and (SCL hostility and SCL psychoticism) (r=-0.325 and P =0.029). There was a positive correlation between SODs and (SCL somatization and SCL paranoia). Table 5

Table 5: Correlation between Oxidized LDL and SODs and other variables of the studied group 1

		Oxidized LDL	SODs
Age (years)	r	-0.061	0.189
	p	0.692	0.215
Somatic GHQ	r	-0.041	0.166
	p	0.788	0.276
Anxiety GHQ	r	-0.117	-0.123
	p	0.443	0.420
Social GHQ	r	-0.140	0.100
	p	0.359	0.511
Severe depression GHQ	r	-0.027	-0.121
	p	0.862	0.428
Score	r	-0.221	-0.017
	p	0.144	0.914
BDIII score	r	-0.126	-0.044
	p	0.411	0.776
SCL somatization	r	-0.268	0.409
	p	0.076	0.005*
SCL-OCD	r	-0.325	0.338
	p	0.029*	0.023
SCL interpersonal sensitivity	r	-0.251	-0.063
	p	0.097	0.680
SCL depression	r	-0.038	-0.065
	p	0.804	0.671
SCL anxiety	r	-0.281	-0.006
	p	0.061	0.967
SCL hostility	r	-0.017	-0.362
	p	0.913	0.015*
SCL phobia	r	0.121	-0.237
	p	0.428	0.118
SCL paranoia	r	-0.090	0.405
	p	0.558	0.006*
SCL psychoticism	r	0.063	-0.351
	p	0.679	0.018*
SODs	r	0.038	--
	p	0.804	--

r: Pearson coefficients. *Significant as P value ≤0.0. BDI: Beck Depression Inventory, STAI: State-Trait Anxiety Inventory, SCL: Symptom Checklist, GHQ: General health questionnaire, OCD: Obsessive-compulsive disorder, SODs: Super oxide dismutase.

Sex (female) and educational level (high) were significantly lower in negative group than positive group (P<0.05). Marital status, BDI-II-degree score and STAI-state were insignificantly different between both groups. STAI-Trait (moderate-severe) and SCL score interpretation (needs treatment) were significantly higher in negative group than positive group (P<0.05). Table 6

Table 6: Relation between SODs and baseline parameters, BDI-II degree, STAI-state, STAI-Trait and SCL score interpretation of the studied groups

		SODs		P
		Negative(n=47)	Positive (n=43)	
Sex	Male	14 (29.79%)	3 (6.98%)	0.006*
	Female	33 (70.21%)	40 (93.02%)	
Educational level	Secondary	11 (23.4%)	0 (0%)	0.001*
	High	36 (76.6%)	43 (100%)	
Marital status	Single	18 (38.3%)	16 (37.21%)	0.227
	Married	26 (54.17%)	27 (61.36%)	
	Divorced	3 (6.38%)	0 (0%)	
		Negative (n=39)	Positive (n=6)	
BDI-II degree	Mild	11 (28.21%)	4 (66.67%)	0.063
	Moderate	28 (71.79%)	2 (33.33%)	
STAI-state	High anxiety	16 (41.03%)	4 (66.67%)	0.412
	Moderate-severe	17 (43.59%)	2 (33.33%)	
STAI-Trait	High anxiety	17 (43.59%)	6 (100%)	0.019*
	moderate-severe	18 (46.15%)	0 (0%)	
SCL score interpretation	Needs treatment	17 (43.59%)	0 (0%)	0.040*
	No	22 (56.41%)	6 (100%)	

Data are presented as frequency (%). *Significant as P value ≤0.0. BDI: Beck Depression Inventory, STAI: State-Trait Anxiety Inventory, SCL: Symptom Checklist, SODs: Super oxide dismutase.

Discussion

Depression is common but underdiagnosed and treated. Recognition and treatment of mild cases might prevent a substantial proportion of future serious cases. Furthermore, depressive disorders that do not meet diagnostic criteria for major depression as well as those only just meeting criteria are associated with significant morbidity, functional impairment and reduced quality of life [16].

Patients with MDD showed a) significantly decreased RCT (mainly lowered high-density lipoprotein cholesterol and paraoxonase 1); b) lowered lipid soluble vitamins (including vitamin A, D, and coenzyme Q10); c) increased lipid peroxidation and aldehyde formation, mainly increased malondialdehyde (MDA),. The ratio of all lipid peroxidation biomarkers/all lipid-associated antioxidant defenses was significantly increased in MDD. In the same line, Bonifaceo et al. [17] proved that activated Oxidative and Nitrosative pathways including increased lipid peroxidation and protein oxidation, which indicates oxidative stress, are the most important predictors of an increased BP, especially in patients with mood disorders. These findings support our hypothesis that depression is linked to oxidative stress and then to various systemic pathologies. In a recent study, Cardon et al. [18] focused on cellular and mitochondrial (dys)function in two atypical cases: an antidepressant non-responding MDD patient and another with an unexplained mitochondrial disorder. Skin biopsies from these patients and controls were used to generate various cell types, including astrocytes and neurons, and cellular and mitochondrial functions were analyzed.

On the other hand, we studied the association of severity of depression and oxidative stress markers, through correlating the severity of depression using psychometric measures as BDI –II and symptom check list -90 along with results of oxidative stress markers. Our results showed no association between the severity of depression and the levels of oxidative stress markers. These results are in the same line with other similar studies, Poletti et al. [19] highlights the importance of screening and early detection of depression irrespective of its severity. Nevertheless, a meta-analysis by Wang et al. [20] found that the positive effect of antioxidant supplementation, such as magnesium, zinc, selenium, CoQ10, tea and coffee and crocin, on depressive status were all significant. And antioxidant supplementation also showed significant improvement in anxiety.

These results are in the same line with our results entails the important relation between depressive disorders and oxidative stress in both directions; as a cause and a result, and that treatment of any of these conditions could lead to improvement of the other performing a safer cellular environment and decrease the possibility of

affection by various serious pathologies.

Moreover, we studied the relation between the state and traits of anxiety with oxidative stress markers using STAI state and trait anxiety inventory, we found that the severity of both state and trait anxiety was associated with lower SOD levels indicating higher oxidative stress state. These findings were proven in previous similar studies. In 2020, Seyed et al. [21] recruited Sixty patients with panic disorder according to the DSM-5 diagnostic criteria for a panic attack and 60 healthy individuals were included in the present study. Oxidative stress indices including glutathione and glutathione peroxidase were investigated. The results indicated decreased serum glutathione concentration and glutathione peroxidase activity in patients.

Nevertheless, we studied the relation between oxidative stress state and somatic symptoms. We found through using SCL-90 questionnaire a direct correlation between level of SOD (antioxidant) and the presence of somatic symptoms such as headache and body aches. On the other hand, we studied the relation between somatic symptoms and Oxidized LDL, we found that there was no direct relation between high levels of oxidized LDL and the presence of somatic symptoms. Unlike our study, Kabadayi et al. [22] studied the relation between somatic symptom disorder and oxidative stress state. The study included 41 medication-free patients with somatic symptom disorder and 47 age, sex, and sociodemographic-matched healthy individuals.

Limitations of the study included that the sample size was relatively small. only two oxidative stress markers, future studies may involve other oxidative stress markers. High cost of oxidative stress marker kits.

Conclusion

The severity of oxidative stress state was not correlated to severity of depression. This study's results go in concomitance with previous studies' results regarding the proven association between MMD and oxidative stress state, lack of association between degree of severity of both conditions, and the confirmed association of anxiety trait to oxidative stress state.

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