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ROLE OF OXIDATIVE STRESS AND NEUROTRANSMITTER IMBALANCE IN DEPRESSION AMONG MEDICAL STUDENTS IN PAKISTAN

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ABSTRACT

Background: Depression in medical students is a growing mental health issue of relevance in many countries, including Pakistan, where academic stress, emotional load, sleep deprivation and institutional inadequacies can be crucial in causing depression in students. Besides the psychosocial factors, it is increasingly becoming clear that the biological cause of depression may play a role in oxidative stress and imbalance of neurotransmitters. Nonetheless, there is a paucity of information reviewing these mechanisms amid medical students in Pakistan.

Objective: To assess how oxidative stress and neurotransmitter imbalance correlate with depression in medical students in Pakistan.

Methods: This analytical cross-sectional study was carried out at Liaquat University of Medical and Health Sciences, Jamshoro between March 2024 and February 2025 among 120 undergraduate medical students of selected medical colleges in Pakistan. The patient health questionnaire-9 was used to measure depression. Blood was evaluated on the markers of oxidative stress, such as malondialdehyde, superoxide dismutase, reduced glutathione and biomarkers related to neurotransmitters, such as serotonin, dopamine, and norepinephrine. Demographic, academic and lifestyle factors were as well documented. The SPSS version 26 was used to perform statistical analysis.

Results: Forty six (38.3%) students were found to be depressed. The levels of malondialdehyde of depressed students were significantly high and considerably lower levels of superoxide dismutase, reduced glutathione, serotonin, dopamine and norepinephrine levels were found among non-depressed students ($p<0.001$). Sleep deprivation, high academic stress and low physical activity were also strongly linked to depression. The scores of patient health questionnaire-9 were correlated positively with malondialdehyde and negatively with antioxidant and neurotransmitter ones.

Conclusion: Oxidative balance and neurotransmitter regulation disturbances seem to be related to depression in medical students in Pakistan. These results suggest a more general biological role in depression among populations of academically stressed students and the necessity of early diagnosis and preventive psychiatric measures.

Keywords: Depression, Oxidative stress, Neurotransmitters, Medical students, Serotonin

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INTRODUCTION

Depression is a common mental health condition among young adults and is increasingly recognised in the academic setting, especially among medical students.[1] The rigorous nature of medical education places students under prolonged academic stress, frequent testing, sleep

deprivation, emotional distress, and performance pressures. This makes medical students more susceptible to mental health issues, including depression, anxiety, burnout and low quality of life compared to other students. In Pakistan, the prevalence of depression among medical students is further exacerbated by sociocultural pressures, lack of formal mental health services, financial stressors, and fierce competition in medical schools.[2]

Historically, depression among medical students has been considered a psychosocial phenomenon resulting from environmental and academic pressures.[3] But recent research in the fields of neurobiology and psychoneuroimmunology has underscored the significance of biological factors in the onset and progression of depression. One such mechanism is oxidative stress, which plays a significant role in the dysfunction of neurons and mood regulation. Oxidative stress is a state of imbalance between the generation of reactive oxygen species (ROS) and antioxidant mechanisms. The brain is highly vulnerable to oxidative stress because of its high oxygen demand and abundant lipid content. Elevated levels of ROS can cause lipid peroxidation, protein oxidation, DNA damage, and disruption of neuronal signaling pathways, which may play a role in the development of depression.[4]

Meanwhile, the monoamine neurotransmitter theory continues to be a key biological model of depression.[5] Serotonin, dopamine, and norepinephrine are key neurotransmitters involved in the regulation of mood, cognition, motivation, reward, and emotional stability. Alterations in these neurotransmitters have been implicated in depressive symptoms such as low mood, anhedonia, lethargy, poor concentration, and sleep disturbances. Oxidative stress and inflammation can affect the synthesis, release, receptor binding, and reuptake of neurotransmitters, providing a link between biochemical stress and neurochemical dysfunction.[6]

Crucially, oxidative stress and neurotransmitter dysfunction are not isolated events.[7] Psychological stress, which is prevalent among medical students, can trigger neuroendocrine responses, including activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated levels of cortisol and reactive oxygen species. This can lead to compromised antioxidant mechanisms and altered monoaminergic pathways, thereby perpetuating a vicious cycle of depression. Other lifestyle factors that are prevalent among medical students, such as poor sleep, diet, exercise and high caffeine consumption, may also exacerbate oxidative stress and neurotransmitter dysfunction.[8]

While there is a burgeoning global interest in the biological underpinnings of depression, there is a paucity of information from Pakistan regarding the interplay between oxidative stress and monoaminergic imbalance in medical students.[9] The majority of these studies have relied mainly on psychological measures without incorporating biochemical markers that could offer additional insights into the underlying mechanisms of the disease. This knowledge is crucial for the development of more holistic approaches to enhance the mental well-being of students.[10-12]

Hence, purpose of the current study was to assess the contribution of oxidative stress and neurotransmitter dysfunction in depression among medical students in Pakistan. Through the measurement of key oxidative stress markers and neurotransmitter levels and their association with the severity of depressive symptoms, this study seeks to gain a more comprehensive view of depression as a complex condition that is influenced by both psychological and biological factors.

MATERIALS AND METHODS

This analytical cross-sectional study was carried out at Liaquat University of Medical and Health Sciences, Jamshoro between March 2024 and February 2025 among 120 undergraduate medical students of selected medical colleges in Pakistan. First to final year medical students (MBBS) were invited to take part in the study. Students of both sexes between the ages of 18 and 26 years were included. Students were included if they were enrolled in a medical college in Pakistan, consented to fill out the psychological screening questionnaire, and consented to have a blood sample taken for biochemical analysis. The study was conducted in line with the Declaration of Helsinki. Informed consent was taken from all participants prior to data collection. The study was voluntary and the confidentiality of participant and laboratory data was maintained at all times.

The students had a history of a psychiatric disorder other than depression, were currently taking antidepressants, anxiolytics, antipsychotics, or any other neuroactive drugs that may affect neurotransmitter levels, or had a history of chronic systemic illness such as diabetes mellitus, thyroid disease, autoimmune disease, chronic liver disease, renal disease, epilepsy, or any acute infectious or inflammatory illness at the time of data collection, history of substance abuse, recent hospitalisation, or unwilling to participate were excluded.

The demographic, academic, lifestyle and clinical factors were collected. This included age, gender, academic year, body mass index (BMI), average hours of sleep, self-reported academic stress, physical activity, smoking, and family history of depression. Academic stress was measured by self-report according to subjective academic stress, exam stress, and study anxiety.

Depression was measured by the Patient Health Questionnaire-9 (PHQ-9), a reliable and valid measure of depressive symptoms. The PHQ-9 is a nine-item questionnaire, rated on a scale of 0-3, with a total score of 0-27. Students were classified into groups based on standard interpretation, and for the purpose of analysis, the sample was divided into two sub-groups: students with depression and students without depression. A score of 10

or more on the PHQ-9 was used to define clinically significant depressive symptoms.

Biochemical analysis involved the collection of about 5 mL of fasting venous blood from each participant under sterile conditions. Biochemical analysis was conducted in the institutional laboratory following standard laboratory procedures. Biochemical assessment was conducted in two broad areas: markers of oxidative stress and markers of neurotransmitters.

Oxidative stress markers included malondialdehyde (MDA) as a marker of lipid peroxidation, superoxide dismutase (SOD) as a marker of enzymatic antioxidant activity, and reduced glutathione (GSH) as a marker of endogenous antioxidant status. These markers were chosen to give a comprehensive picture of oxidative stress and antioxidant status, which are believed to be involved in the neurobiology of depression.

To evaluate neurotransmitter dysfunction, we measured the serum concentrations of serotonin, dopamine and norepinephrine. These were chosen based on their known roles in mood, emotion, motivation, reward, and stress. These biochemical markers were measured using enzyme-linked immunosorbent assay (ELISA) kits and conventional spectrophotometric methods according to the manufacturers' instructions.

Data were entered and analysed using SPSS-26. The mean values of biochemical markers were compared between depressed and non-depressed students using the independent sample t-test. The Chi-square test was also used to assess the association between qualitative variables. Furthermore, Pearson correlation was used to assess the correlation between PHQ-9 depression scores and biochemical parameters. A p-value of less than 0.05 was considered statistically significant.

RESULTS

According to the PHQ-9 scoring system, 46 students (38.3%) were classified as depressed and 74 students (61.7%) were classified as non-depressed. The mean age of the study participants was 21.2±1.7 years (range 18-26 years). A total of 68 (56.7%) were females and 52 (43.3%) were males. There were more female students in the depressed group than males. Likewise, students with low sleep duration, high academic stress and low physical activity were more prevalent in the depressed group. The average PHQ-9 score was much higher in the depressed group, suggesting a clear separation of symptoms between study groups. The depression in medical students may be associated with certain demographic and lifestyle factors. The age and the BMI were marginally more in the depressed group; however, the difference was not statistically significant. Nevertheless, the likelihood of sleep deprivation among students with depression as well as the levels of academic stress and decreased physical activity was significantly higher among depressed students than among non-depressed students. The percentage of females was also numerically more in the depressed group but the difference was not statistically significant in the current sample. The reliability of the clinical categorization adopted in this research is confirmed by the substantially high PHQ-9 score in the depressed group (Table 1).

Although 23.3 percent of students had few or no symptoms, a significant proportion of students had some characteristics of mildly depressive incidents, and almost one-third of the overall sample had a clinically significant character on moderate to severe depression. These results show the high emotional stress driven by medical students and the necessity of early detection and proactive mental health measures within academic institutions (Table 2).

The biochemical difference between the two groups of study is very clear in table 3. Depressed students recorded a considerable increase in MDA, which signifies a higher level of oxidative damage, whereas SOD and GSH were decreased considerably, thus portraying a disabled ability of antioxidants buffering capacity. Simultaneously, depressed students had reduced serotonin, dopamine and norepinephrine circulating indicating a trend in neurochemical dysregulation, which is congruent with the depressive pathophysiology. The concomitants of increased oxidative stress with a low level of neurotransmitters in the depressed group favor the assumption that these biological systems could be interconnected. In order to find out more about the connection between biochemical changes and the level of depression, correlation analysis between PHQ-9 score and each of the laboratory parameters was conducted.

Table 1: Baseline characteristics of medical students according to depression status

Variable	Total (n=120)	Depression Present (n = 46)	No Depression (n = 74)	p-value
Age (years)	21.2±1.7	21.4±1.6	21.0±1.8	0.228
Female	68 (56.7%)	30 (65.2%)	38 (51.4%)	0.141
Male	52 (43.3%)	16 (34.8%)	36 (48.6%)	0.141
BMI (kg/m²)	23.5±3.1	24.0±3.3	23.1±2.9	0.109
Sleep <6 hours/day	49 (40.8%)	29 (63%)	20 (27%)	<0.001
High academic stress	76 (63.3%)	37 (80.4%)	39 (52.7%)	0.002
Low physical activity	58 (48.3%)	31 (67.4%)	27 (36.5%)	0.001
Family history of depression	21 (17.5%)	11 (23.9%)	10 (13.5%)	0.151
PHQ-9 score	8.6±5.0	14.1±2.8	5.2±2.3	<0.001

Table 2: Distribution of depression severity based on PHQ-9 score

PHQ-9 Category	No.	%
Minimal / None (0–4)	28	23.3
Mild (5–9)	46	38.3
Moderate (10–14)	24	20.0
Moderately Severe (15–19)	16	13.3
Severe (20–27)	6	5.0

Table 3: Comparison of oxidative stress and neurotransmitter biomarkers between students with and without depression

Biomarker	Depression Present (n = 46)	No Depression (n = 74)	p-value
MDA (nmol/mL)	4.81±0.82	3.46±0.69	<0.001
SOD (U/mL)	1.84±0.37	2.39±0.44	<0.001
GSH (µmol/L)	3.74±0.76	4.96±0.88	<0.001
Serotonin (ng/mL)	78.9±14.6	103.5±17.8	<0.001
Dopamine (pg/mL)	44.1±8.9	57.6±10.1	<0.001
Norepinephrine (pg/mL)	184.7±27.1	226.4±30.8	<0.001

Table 4: Correlation of PHQ-9 depression score with oxidative stress and neurotransmitter biomarkers

Variable	Correlation Coefficient (r)	p-value
MDA	+0.59	<0.001
SOD	-0.47	<0.001
GSH	-0.54	<0.001
Serotonin	-0.62	<0.001
Dopamine	-0.50	<0.001
Norepinephrine	-0.44	<0.001

The results of the analysis showed that the severity of the depression increased significantly with the deteriorating oxidative stress and the decrease in the level of neurotransmitters. In particular, MDA had a positive relationship with PHQ-9 score, but SOD, GSH, serotonin, dopamine, and norepinephrine had negative relationships with the severity of depressive symptoms (Table 3).

Table 4 shows that it was not only the clinical measure of severity of depression, but it was also synonymous with biochemical imbalance underlying the problem. The students who scored higher on PHQ-9 were more likely to experience stronger oxidative stress as well as significant decreases in antioxidant and neurotransmitter markers. Serotonin had the highest negative association with the severity of depression, then GSH and dopamine and MDA had the strongest positive relationship. This trend indicates that deteriorating depressive symptoms could be an expression of neurochemical inadequacy and augmented oxidative charge.

DISCUSSION

The current research tested the effect of oxidative stress and the imbalance of neurotransmitters on depression in medical students in Pakistan and proved that the biological profile of depressive students was significantly different as compared to non-depressive students. Particularly, depression was linked to an increase in malondialdehyde (MDA) levels, a decrease in antioxidant defenses (serotonin, reduced superoxide dismutase (SOD), and glutathione (GSH)) and a significant decrease in the levels of such mood-related neurotransmitters as serotonin, dopamine, and norepinephrine. Moreover, depression in this sample was more prevalent in those students who noted sleeping deprivation, increased academic stress and reduced physical exercise and points to the depressive symptoms of medical students as being possibly due to the interplay of both psychosocial and biological factors. This is in line with larger literature that depression among students is prevalent in Pakistan and stressful academic conditions can be significant contributors of emotional morbidity.[2,3]

The fact that the level of MDA was much higher in depressed students was one of the most significant discoveries of the current research.[4] MDA is an accepted lipid peroxidation marker and is an indicator of cell membrane oxidative damage. High levels of MDA in the depressed group indicate that there is a possibility of greater oxidative damage in the systemic level in these students. This finding is biologically reasonable as chronic stresses and disturbances in sleep, abnormal eating habits and extended mental loads, all of which are typical of medical training, may elevate reactive oxygen species generation and reduce the effectiveness of inherent antioxidant defenses. Oxidative stress in the context of depression could be involved in neuronal dysfunction, impaired synaptic plasticity, altered membrane fluidity, stress in the mitochondrion and neuroinflammatory activation. Modern reviews are becoming more inclined towards the notion that depression is a neurotransmitter disorder, but it is a disease characterized by oxidative, metabolic and neuroimmune dys regulation.[6]

Alongside increased oxidative damage, the current study has also observed a much lower level of SOD and GSH in depressed individuals.[7] This observation is especially significant since these two markers are the key aspects of the antioxidant defense mechanism of the body. SOD is a protective molecule and is able to break the superoxide radicals down into less dangerous molecules whereas GSH is an important intracellular antioxidant that is used in the detoxification process and redox holding. The low concentrations of these markers among depressed students indicate that they may be unable to neutralize oxidative stress because their biological ability to do so might have been compromised.[8] This compromised antioxidant defense can expose neuronal tissues to increased susceptibility to stress-related damage and may contribute to the reason why specific students develop the enduring depressive symptoms when under academic stress whereas others may be comparatively resistant.[9]

The other important observation made in the current research was that the levels of serotonin, dopamine, and norepinephrine were significantly lower in students who were depressed. These neurotransmitters play a key role in mood control, emotional stability, motivation, concentration, sleep, appetite, reward processing and coping to stress. Reduced serotonin levels can be associated with sadness, emotional regulation problems, and sleeping disturbance, reduced dopamine levels may be associated with decreased motivation, fatigue, poor attention, and anhedonia, and reduced norepinephrine levels may be related to poor alertness, diminished energy, inability to handle academic stress. These close inverse relationships between these neurotransmitters and PHQ-9 scores indicate that an increasing number of neurochemical dysregulation can be associated with the worsening symptoms of depressive state among medical students. These results are consistent with the old monoamine model of depression, and also with the newer ones where the dysfunction of neurotransmitters is determined by oxidative and other stress-induced physiologic alterations.[11,12]

The main conceptual strength of this study is that the authors did not consider the neurotransmitter imbalance and oxidative stress independently but as one. The trend that is observed is that these systems are potentially biologically related. Neurotransmitter synthesis, vesicular storage, receptor signaling, and neuronal membrane integrity can be interfered with by oxidative stress. Simultaneously, this can be accompanied by a decreased adaptation rate to stress, an inability to control emotions, and a lack of behavioral resilience, which predisposes individuals to chronic distress. Thus, the results of the current research confirm the hypothesis of the biopsychosocial theory of depression, where the academic load and the lifestyle factors of stress interact with the quantifiable biochemical disruptions to regulate the mood and mental health.[13,14]

Again, the current study established that students who were depressed had significantly higher chances of reporting on the sleeping duration (less than 6 hours), high academic stress, and low physical activity. Such results are very applicable in medical education. It has been established that sleep deprivation leads to impairment of emotional regulation, cortisol release, neurotransmitters homeostasis and oxidative burden. In a similar manner, long-term academic stress can stimulate the hypothalamic-pituitary-adrenal axis, increase free radicals, and increase neurochemical imbalance. The associated decreased body activity can further worsen depressive symptoms by decreasing the level of endorphin release, decreasing antioxidant ability and diminishing the resilience to stresses.[15,16] Other research on student mental health has found that depression has been associated with these lifestyle factors that are open to change in the past, which contradicts the improbability of the current results.[17]

Even though the percentage ratio of depression among the female students in the current study was statistically significant with respect to the baseline comparison, the difference was not very strong. Nevertheless, the tendency is also clinically significant, and it still follows the literature that postulates that female students tend to report a greater proportion of depressive symptoms, emotional distress, and stress-associated burden. This can be an expression of a convergence of biological vulnerability, a sociocultural expectation, internalized stress, a difference in coping style, and a reporting pattern. However, the biochemical trend of change in the current research was similar in the two sexes in general, suggesting that the relationship between depression and oxidative stress as well as neurotransmitter imbalance is not exclusive to a particular sex.[18,19]

The rates of depression that are witnessed in this study are also striking and generally in line with the larger body of literature that indicates that medical students are a psychologically vulnerable population. Systemic reviews and Pakistani student data have shown that depressive symptoms are very common among university and medical students and they tend to be on levels that can be regarded as a serious educational and health issue. It implies that biological results of the current research are not present in a small minority group, but in a population that is already known to be at high risk of mental health.[20]

The current research has a number of limitations in spite of its strengths. To begin with, cross-sectional design is incapable of causing a conclusion; thus, it could not be established whether the oxidative stress and neurotransmitter imbalance were the direct causes of depression or were the results of the latter. Second, the study depended on one-time-point serum measures, which might not be comprehensive to indicate the dynamic neurobiological status of students during examination periods or during exam stress. Third, serum neurotransmitter levels do not fully indicate

neurotransmission of the central nervous system. Fourth, the research was restricted to med students and might not be applicable to the general populations in universities. Lastly, other biologically useful markers, e.g. cortisol, inflammatory cytokines, brain-derived neurotrophic factor, and indexes of sleep quality, were not addressed and might be considered in future studies.

In spite of such limitations, the study has significant strengths. It deals with an insufficiently studied, yet clinically significant, group in Pakistan and employs an established depression screening instrument, and combines oxidative stress biomarkers with neurotransmitter-based biomarkers in the same research design. This gives a deeper insight into the mental status of depression in medical students and gives the evidence that can be used to assist in the future prevention measures and screening of student mental health.

CONCLUSION

Depression among medical students is linked to considerable oxidative stress and neurotransmitter imbalance. The levels of MDA and antioxidant defenses were higher in depressive symptomatic students who also had lower levels of serotonin, dopamine, and norepinephrine than the non-depression students. Poor sleep, high academic stress, and low physical activity were also found to be significantly linked with depression meaning that the behavioral and biological factors can potentially influence the emotional morbidity of this population.

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