Original Article

Association of Serum Cortisol, Interleukin-6, and Serotonin with Depression

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ABSTRACT

Objective: To explore the relation between serum cortisol, interleukin-6 (IL-6), and serotonin (5-HT) levels in patients with melancholic depression, atypical depression, and healthy controls.

Methodology: This cross-sectional comparative study was conducted from August 2023 to July 2024 at the Combined Military Hospital, Muzaffarabad. After ethical approval of the study, a total of 105 participants were enrolled using a non-probability convenience sampling method, including 35 healthy individuals, 35 with melancholic depression, and 35 with atypical depression. Serum levels of cortisol, IL-6, and serotonin were measured using enzyme-linked immunosorbent assay. The Statistical Package for the Social Sciences (SPSS) version 25 was used to analyze the data and determine associations between these biomarkers across different depression groups.

Results: Elevated serum IL-6 levels were found in both depression groups compared to healthy controls ($p < 0.001$). Serum cortisol levels were significantly higher in both depression groups as compared to controls, with a notable difference between the two depression types ($p < 0.001$). Serum serotonin levels were lower in both depression groups as compared to controls with no significant variation between melancholic and atypical depression ($p < 0.001$). Positive correlations were observed between serum IL-6 and cortisol ($p = 0.001$; $r = 0.629$) in melancholic depression, while IL-6 exhibited a negative correlation with serotonin ($p = 0.014$; $r = -0.411$) in atypical depression. Serum cortisol also displayed a negative correlation with serotonin in melancholic depression but the results were statistically insignificant ($r = -0.33$, $p = 0.05$).

Conclusion: This study revealed elevated cortisol & interleukin-6 levels and decreased serotonin levels in depression groups as compared to healthy controls. The melancholic & atypical depression subtypes did not significantly differ for interleukin-6 and serotonin levels. However, a significant elevation in serum cortisol levels was observed in patients with melancholic depression versus those with atypical depression.

Keywords: *Depression. Cortisol. Interleukin-6. Serotonin. Biomarkers.*

INTRODUCTION

Major depressive disorder (MDD) is commonly referred to as clinical depression and it is among the most prevalent psychiatric disorders, impacting around 280 million individuals globally.[1] The condition is more than just occasional sadness or mood fluctuations; it is a serious illness that can severely impair an individual's ability to carry out daily tasks, leading to poor quality of life. Depression often disrupts personal relationships and professional life, which can result in social isolation and the deterioration of self-esteem.[2] Importantly, depression is the primary psychiatric condition linked to suicide, with patients exhibiting the highest suicidal tendencies among those with mental health disorders.[3] Furthermore, untreated depression is associated with the early onset of various systemic diseases, including cardiovascular diseases, and can reduce life expectancy by up to seven years.[4]

It is identified by a persistent low mood lasting a minimum of two weeks, along with symptoms such as anhedonia (loss of interest or pleasure), low self-esteem, feelings of guilt, changes in appetite, sleep disturbances, and persistent fatigue.[5] It typically occurs in an individual's thirties, with a second peak in the fifties. The disorder also exhibits varying frequencies among different socio-economic and gender groups, with women and those in low socioeconomic strata more likely to experience depressive episodes.[6]

Melancholic and atypical depression are two subtypes of major depressive disorder. Melancholic depression is often marked by a loss of interest in activities that were once enjoyable, psychomotor retardation, weight loss, and anhedonia. Suicidal thoughts are common among individuals with this subtype.[7] Atypical depression is characterized by emotional reactivity, excessive sleep, weight gain, and leaden paralysis (feelings of heaviness in the limbs).[8]

The pathophysiology of depression encompasses a complex interplay among environmental, genetic, and neurobiological factors. Empirical evidence indicates a correlation between depression and the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, immune responses, and the serotonergic

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Received: April 10, 2025; Accepted: May 23, 2025

system.[9] Elevated interleukin-6 levels and disturbances in serotonin metabolism have been shown to contribute specifically to the pathogenesis of depression. Interleukin-6 is believed to affect serotonin production by activating the indoleamine 2,3-dioxygenase pathway, which results in decreased serotonin levels.[10] Additionally, the HPA axis, responsible for regulating the body's stress response, is frequently overactive in individuals with depression. This leads to increased cortisol levels, which may further worsen depressive symptoms.[11]

This study planned to evaluate the levels of serum cortisol, IL-6, and serotonin in patients with melancholic depression, atypical depression, and healthy controls. Previous studies did not analyze these markers collectively so, we measured these biochemical markers in two distinct subtypes of MDD, i.e. melancholic and atypical depression. Identifying these biomarkers could offer insights into the pathophysiology of depression and contribute to more effective & personalized treatment strategies for the diverse population of Pakistan.

METHODOLOGY

This cross-sectional comparative study was conducted from August 2023 to July 2024 at the Combined Military Hospital, Muzaffarabad. The biochemical assays and data analysis were performed at the Biochemistry Department, University of Health Sciences, Lahore after the approval of the project from advanced studies and research board (Letter No. UHS/REG-23/ERC/3142, 20-06-2023). The required sample size was calculated by the World Health Organization (WHO) sample size calculator, ensuring a study power of 96% and a significance level of 5%. The anticipated mean±standard deviation (SD) cortisol levels for group 1 (cases) and group 2 (healthy controls) were 11.92±4.2 ng/mL and 8.90±3.4 ng/mL, respectively.[4] Based on these parameters, the minimum sample size for each group was calculated to be 35, resulting in a total sample size of 105. The non-probability convenience sampling technique was used to enroll participants and they were divided into 3 groups with 35 each: melancholic depression, atypical depression and healthy controls. Those aged 18 years or above, patients meeting the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) for melancholic & atypical depression were included in the study.[12] Pregnant females, subjects with organic mental illness or comorbid severe systemic illness were excluded from the study. A structured proforma was used to collect data after taking written informed consent. Healthy hospital controls were enrolled from the attendants of the patients visiting the hospital outpatient department (OPD). Patients visiting psychiatry OPD for depression were interviewed and labeled as having melancholic and atypical depression based on the criteria given in the DSM-5-TR along with psychometric assessments for the severity of depression based on the Beck Depression Inventory-II (BDI-II). According to the DSM-5-TR, early morning awakening, lack of mood reactivity, weight loss, psychomotor changes, and profound anhedonia were the symptoms of melancholic depression. In atypical depression, the patients present with increased appetite, weight gain, hypersomnia, leaden paralysis, mood reactivity, and sensitivity to rejection. Reliable and validated BDI-II has 21 items and each item scored 0-3 with a total score range from 0-63. This scoring shows the severity of depression as follows:

- **0-13:** Minimal depression
- **14-19:** Mild depression
- **20-28:** Moderate depression
- **29-63:** Severe depression[13]

Using aseptic techniques, 5 ml of blood sample was collected in a gel vacutainer between 8:00 AM to 10:00 AM. The sample was centrifugated at 6000 rpm for 10 minutes and serum was separated. The serum was preserved at -80°C before analysis. The levels of serum cortisol, interleukin-6, and serotonin were determined using enzyme-linked immunosorbent assay (ELISA). The Cortisol ELISA kit (Cal-biotech Inc., China, Lot #113324) was used to measure serum cortisol, with the assay based on competitive binding, where color intensity is inversely correlated with cortisol concentration. The IL-6 and serotonin ELISA kit (BT LAB China, Lot#113326 and 113319), used a capture antibody to bind IL-6/ anti-serotonin antibody, followed by horseradish peroxidase (HRP) conjugation and chromogenic substrate reaction. Absorbance readings were taken using a microplate reader (Biorad-450), and concentrations were calculated from standard curves, with cortisol and IL-6 in ng/ml and serotonin in pg/ml.

STATISTICAL ANALYSIS

The data was analyzed using Statistical Package for the Social Sciences (SPSS) version 25. Descriptive statistics were used for continuous variables, while categorical variables were presented as frequencies and percentages. The Chi-square test was applied for the comparison of categorical variables. For

normally distributed data, Analysis of Variance (ANOVA) was used to compare means of three groups and the Kruskal-Wallis test was utilized for non-normally distributed data. The correlation between serum cortisol, IL-6, and serotonin levels was examined using Pearson's correlation tests. A p-value of ≤0.05 was taken as significant.

RESULTS

A total of 105 participants were recruited in this study, comprising 35 in each group of melancholic, atypical depression, and healthy controls. The comparison of presenting symptoms, disease duration, symptom severity, and family history between melancholic and atypical depression groups showed notable trends. Somatic symptoms were more prevalent in both depression groups, 54.3% of patients with melancholic and 65.7% of patients with atypical depression reported these symptoms. In the atypical depression group, only 11.4% of patients presented with cognitive symptoms, whereas, in the melancholic group, 12.9% of patients had cognitive symptoms. Regarding disease duration, 57.1% patients in the melancholic group and 68.6% in the atypical group had been suffering for less than 6 months. Melancholic depression was associated with a greater proportion of severe cases (40%), while atypical depression was primarily characterized by mild symptoms (68.6%). A family history of psychiatric illness was seen in 2.9% patients of melancholic depression and 8.6% patients of atypical depression. There was no statistically significant difference observed between the groups for these variables (p >0.05).

Biomarker analysis revealed significant differences in serum levels of cortisol, serotonin, and IL-6 between the depression groups and healthy controls. Cortisol levels were significantly higher in melancholic depression (194.8±81.3 ng/ml) compared to atypical depression (155.3±61.7 ng/ml) and healthy controls (82.9±25.4 ng/ml) (p-value <0.001). Serotonin levels were significantly lower in both the depression groups (melancholic: 341.6±56.9 pg/ml, atypical: 347.2±83.6 pg/ml) as compared to healthy controls (741.2±89.0 pg/ml) with a p-value of <0.001. Interleukin-6 levels were statistically higher in both depression groups (melancholic: 122.4±66.4 ng/ml, atypical: 118.4±57.0 ng/ml) as compared to healthy controls (66.5±35.5 ng/ml) (p <0.001). A comparison of biomarkers between melancholic, atypical depression, and healthy controls is shown in Table 1.

Serum cortisol and IL-6 levels showed a statistically significant positive correlation in melancholic depression (r=0.629, p=0.001) and healthy controls (r=0.658, p=0.001), whereas no significant correlation was observed in atypical depression (r=0.318, p=0.063). In atypical depression, there was a significant negative correlation between IL-6 and serotonin (r=-0.411, p=0.014) versus melancholic depression or healthy control group. Serum cortisol and serotonin levels showed a significant negative correlation in patients with melancholic depression, whereas, no significant correlations in any other group (Table 2).

DISCUSSION

This study is conducted to determine three key factors considered to contribute to the development of depression: cytokines, stress hormones, and neurotransmitters. We found significantly higher serum cortisol and IL-6 levels & low serotonin levels in melancholic & atypical depression versus the healthy control group (p <0.001). These findings align with previous studies showing elevated IL-6 levels in MDD, reinforcing the concept that inflammation has a contributing role in the disorder's pathophysiology.[14]

Table 1: Comparison of Biomarkers between Melancholic, Atypical Depression, and Healthy Controls

Biochemical Markers	Melancholic Depression	Atypical Depression	Healthy Controls	p-value
	Mean±SD			
Serum Cortisol Levels (ng/ml)	194.8±81.3	155.3±61.7	82.9±25.4	<0.001*
Serum Serotonin Levels (pg/ml)	341.6±56.9	347.2±83.6	741.2±89.0	<0.001*
Serum IL-6 Levels (ng/ml)	122.4±66.4	118.4±57.0	66.5±35.5	<0.001*

**Significant p-value*

Table 2: Correlation Analysis of Serum Biomarkers in Different Groups

Groups	Parameters	Correlation Coefficient	p-value
Melancholic Depression	**Serum IL-6 Levels Serum Cortisol Levels**	0.629	0.001*
Atypical Depression	**Serum IL-6 Levels Serum Cortisol Levels**	0.318	0.063
Healthy Controls	**Serum IL-6 Levels Serum Cortisol Levels**	0.658	0.001*
Melancholic Depression	**Serum IL-6 Levels Serum Serotonin Levels**	-0.155	0.374
Atypical Depression	**Serum IL-6 Levels Serum Serotonin Levels**	-0.411	0.014*
Healthy Controls	**Serum IL-6 Levels Serum Serotonin Levels**	0.041	0.814
Melancholic Depression	**Serum Cortisol Levels Serum Serotonin Levels**	-0.33	0.05
Atypical Depression	**Serum Cortisol Levels Serum Serotonin Levels**	0.295	0.086
Healthy Controls	**Serum Cortisol Levels Serum Serotonin Levels**	0.008	0.962

**Significant p-value*

In depression, the innate immune system remains chronically activated, producing elevated levels of IL-6 and similar inflammatory mediators, which can interfere with neurotransmitter function, induce glucocorticoid resistance, and trigger maladaptive behaviors.[2,15] On the contrary, another study involving 4756 women found no significant relationship between IL-6 levels and depression incidence over 6-18 years, suggesting variability in findings depending on study design and population.[16]

Despite the significant elevation of IL-6 in both depression subtypes, our study found no distinction between melancholic and atypical depression regarding IL-6 levels. Another study observed no significant differences in IL-6 levels between depression subtypes.[17]

In this study, we observed a significant increase in serum cortisol levels in both melancholic (194.8±81.3 ng/mL) and atypical depression (155.3±61.7 ng/mL) as compared to controls (82.9±25.4 ng/mL) with a significant difference between the two depression subtypes ($p < 0.001$). Elevated cortisol levels in depression have also been depicted by Levi et al. and Patil et al.[18,19] Cortisol dysregulation is often linked to the HPA axis' impaired response to stress, and prolonged cortisol elevation can contribute to the maladaptive stress responses seen in depression. Moreover, melancholic depression may be characterized by more pronounced HPA axis hyperactivity.[19] In our study, melancholic depression exhibited significantly higher cortisol levels compared to atypical depression. Another study found that cortisol levels were significantly elevated in the depression group compared to healthy controls ($p=0.008$). However, no significant differences were observed between the group with depression and the psychiatric diseases group Additionally, cortisol levels were notably higher in individuals with depression ($p=0.004$) and in those with two or more suicide attempts ($p < 0.001$).[20]

The current study also measured serum serotonin levels. The mean serum serotonin (5-HT) levels were higher in healthy controls (741.2±89.0 pg/mL) compared to diseased patients with melancholic (341.6±56.9 pg/mL) and atypical depression (347.2±83.6 pg/mL) ($p < 0.001$). Our findings are in line with the theory that serotonin depletion in depression may be linked to immune system activation and the inflammatory response, which can suppress serotonin synthesis.[21] This is consistent with previous research by Colle et al. showing that individuals with depression have significantly lower serotonin levels compared to those without depression.[22] Obermanns et al. reported that depressed patients have lower levels of serotonin in both platelets and serum.[21] Cytokines like IL-6 are implicated in the suppression of serotonin synthesis through the activation of the enzyme indoleamine 2,3-dioxygenase, which diverts serotonin precursors to kynurenine instead of serotonin.[23] This process helps explain the lower serotonin levels observed in depression, as cytokines also modulate serotonin reuptake and metabolism.[24]

In this study, we found that interleukin-6 levels were statistically higher in both depression groups (melancholic: 122.4±66.4 ng/ml, atypical: 118.4±57.0 ng/ml) as compared to healthy controls (66.5±35.5 ng/ml) ($p < 0.001$). These findings align with those reported in recent studies. Koutentaki et al. and Li et al. reported a significant positive correlation between IL-6 and cortisol in patients with depression, supporting the idea that immune system activation via cytokines, such as IL-6, can stimulate the release of cortisol.[25,26]

Regarding serotonin, we found a significant negative correlation between IL-6 and serotonin in the atypical depression group ($r=-0.411$; $p=0.014$), similar to the study conducted by Falcicchia et al. which suggested that cytokines, including IL-6, may reduce serotonin production through the activation of the indoleamine 2,3 dioxygenase enzyme, which diverts tryptophan metabolism towards kynurenine production instead of serotonin.[27]

This study contributes valuable insights into the role of peripheral serotonin, cortisol, and interleukin-6 levels in the pathophysiology of melancholic and atypical depression. These findings may pave the way for more precise diagnostic approaches and tailored therapeutic strategies, ultimately alleviating the burden of this debilitating condition.

CONCLUSION

This study revealed elevated cortisol & interleukin-6 levels and decreased levels of serotonin in individuals with melancholic & atypical depression versus healthy control group. Serum interleukin-6 and serotonin levels did not change significantly in both melancholic & atypical depression subtypes. However, serum cortisol levels were significantly higher in the melancholic depression group as compared to atypical depression. A significant positive correlation was found between cortisol and interleukin-6 levels in melancholic depression and a significant negative correlation between IL-6 and serotonin in the atypical depression group and serum cortisol and serotonin levels in the melancholic depression group.

LIMITATIONS & RECOMMENDATIONS

The notable limitations include the cross-sectional study design, small sample size, and the limited cytokine analysis, focusing solely on IL-6. Furthermore, the reliance on morning cortisol samples may not fully reflect the chronic dysregulation of the HPA axis in depression. Future studies with larger sample size, longitudinal design, and a broader range of inflammatory markers are necessary to enhance our understanding of the complex mechanisms underlying MDD and improve clinical outcomes.

Conflict of interest: None.
Source of funding: None.

Authors' Contributions:
A.T: Conduct experimental work, sample collection, and manuscript writing.
F.B: Study planning and manuscript review.
M.H.K: Patient selection and manuscript review.
M.A.S: Manuscript writing and critical analysis of findings.
N.W: Methodology drafting and implementation of study techniques.
A.S: Proofreading, grammar check, and manuscript review
S.H: Manuscript writing and statistical analysis.

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