International Journal of Medicine
pISSN 1468-3814 | eISSN 2667-7008
https://theinternationalmedicine.com/

Original Research Article *DOI: 10.61336/im/26-2-79*

INFLAMMATORY AND ENDOCRINE BIOMARKERS - SERUM CORTISOL LEVEL, FT4, TSH, CRP IN MAJOR DEPRESSIVE DISORDER - AN INSIGHT IN PATHOLOGY

[1]Dr.Ujjwal Bandyopadhyay, [2]Dr.Supti Mukhopadhyay (Banerjee)

[1]MBBS,DPM,MD (Psychiatry) Professor & Head, Department of Psychiatry, ESI-PGIMSR, ESIC Medical College & Hospital, Kolkata.
[2]MBBS,MD(Pathology) Senior Consultant Pathologist, Associate Professor, Department of Pathology,ICARE Institute of Medical Science and Research,Haldia, Proprietor - Rishi Pathological Laboratory, Kolkata

Correspondence:

Received: January 20, 2026
Revised: January 28, 2026
Accepted: February 16, 2026
Published: February 27, 2026

Abstract

Background: Major Depressive Disorder (MDD) is a complex psychiatric condition increasingly recognized as a multisystem disorder involving neuroendocrine and inflammatory dysregulation. Alterations in the hypothalamic–pituitary–adrenal (HPA) axis, hypothalamic–pituitary–thyroid (HPT) axis, and systemic inflammatory markers have been implicated in its pathophysiology. ***Aim:*** To evaluate serum cortisol, free thyroxine (FT4), thyroid-stimulating hormone (TSH), and C-reactive protein (CRP) levels in patients with Major Depressive Disorder and to analyze their association with disease severity. ***Materials and Methods:*** This observational cross-sectional study was conducted at Rishi Pathological Laboratory, Kolkata, over a period of one year. Thirty adult patients diagnosed with MDD were included. Serum cortisol was measured using chemiluminescent immunoassay, FT4 and TSH by automated immunoassay analyzer, and CRP by immunoturbidimetric method. Statistical analysis was performed to assess significance and correlation with severity. ***Results:*** Elevated serum cortisol was observed in 60% of patients (p=0.004), while 70% showed raised CRP levels (p=0.001). Thyroid abnormalities were common, with elevated TSH in 63.3% (p=0.009) and low FT4 in 46.7% (p=0.038). Significant positive correlation was noted between cortisol, CRP, TSH levels and severity of depression. ***Conclusion:*** The study highlights significant inflammatory and endocrine alterations in MDD, supporting the concept of depression as a neuro-immune-endocrine disorder. Biomarker evaluation may aid in better understanding, early detection, and individualized management of depression.

Keywords: Major Depressive Disorder; Serum Cortisol; C-reactive Protein; Thyroid Function Tests; Inflammatory Biomarkers.

INTRODUCTION

Major Depressive Disorder (MDD) is a complex, heterogeneous psychiatric illness characterized not only by persistent low mood, anhedonia, cognitive impairment, and somatic symptoms, but also by profound neurobiological and systemic alterations. Traditionally conceptualized as a disorder of monoaminergic neurotransmission, contemporary research increasingly recognizes depression as a multisystem disease involving dysregulation of inflammatory pathways and endocrine axes. In particular, disturbances in the hypothalamic–pituitary–adrenal (HPA) axis and the hypothalamic–pituitary–thyroid (HPT) axis, along with activation of systemic inflammatory markers such as C-reactive protein (CRP), have emerged as important pathophysiological correlates. The evaluation of biomarkers including serum cortisol, free thyroxine (FT4), thyroid-stimulating hormone (TSH), and CRP provides valuable insight into the biological underpinnings of MDD and may enhance diagnostic precision and therapeutic stratification [1].

The HPA axis is one of the most extensively studied neuroendocrine systems in depression. Chronic psychological stress, a major precipitating factor in MDD, activates the hypothalamus to release corticotropin-releasing hormone (CRH), stimulating adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary, which in turn drives cortisol production from the adrenal cortex. In many patients with MDD, hyperactivity of the HPA axis results in sustained elevation of serum cortisol levels, impaired negative feedback inhibition, and structural changes in limbic regions such as the hippocampus [2]. Elevated cortisol contributes to neuronal atrophy, reduced neurogenesis, and alterations in synaptic plasticity, thereby perpetuating depressive symptomatology. Moreover, abnormal diurnal variation of cortisol and non-suppression in dexamethasone suppression tests further substantiate HPA axis dysregulation in MDD [3].

Parallel to HPA axis abnormalities, thyroid dysfunction is frequently observed in depressive disorders. The HPT

axis plays a crucial role in regulating mood, cognition, and energy metabolism. Subclinical hypothyroidism, altered TSH secretion, and low or low-normal FT4 levels have been reported in subsets of patients with MDD, even in the absence of overt thyroid disease [4]. Thyroid hormones modulate serotonergic and noradrenergic neurotransmission, and reduced thyroid function may exacerbate depressive symptoms. Conversely, elevated TSH levels may reflect impaired feedback mechanisms within the HPT axis, potentially secondary to chronic stress or inflammatory processes. The therapeutic use of thyroid hormone augmentation in treatment-resistant depression further supports the biological relevance of thyroid axis alterations in MDD [5].

Inflammation has emerged as another central mechanism in the pathogenesis of depression. Increasing evidence suggests that MDD is associated with a state of low-grade systemic inflammation, characterized by elevated pro-inflammatory cytokines and acute-phase reactants such as CRP. CRP, synthesized in the liver in response to interleukin-6 (IL-6) stimulation, serves as a reliable and widely accessible marker of systemic inflammation. Elevated CRP levels have been consistently associated with greater severity of depressive symptoms, reduced response to conventional antidepressants, and increased risk of recurrence [6]. Pro-inflammatory cytokines can influence neurotransmitter metabolism, reduce serotonin availability through activation of the indoleamine 2,3-dioxygenase pathway, and impair neuroplasticity, thereby contributing to depressive pathophysiology [7].

Importantly, inflammatory and endocrine pathways are intricately interconnected. Chronic inflammation can stimulate the HPA axis, leading to sustained cortisol release, while prolonged hypercortisolemia may, paradoxically, impair immune regulation and promote glucocorticoid resistance [8]. Similarly, inflammatory cytokines can alter thyroid hormone metabolism by affecting deiodinase activity and TSH secretion, contributing to the "non-thyroidal illness syndrome" frequently observed in chronic diseases and psychiatric disorders [9]. Thus, serum cortisol, FT4, TSH, and CRP should not be viewed as isolated parameters but rather as components of a dynamic neuroimmune–endocrine network underlying MDD.

Understanding the interplay between these biomarkers holds significant clinical implications. Identification of hypercortisolemia or elevated CRP may help stratify patients who are more likely to benefit from anti-inflammatory strategies or stress-modulating interventions. Likewise, detection of subtle thyroid dysfunction may prompt early correction or adjunctive thyroid hormone therapy. Biomarker-based approaches may therefore pave the way toward personalized psychiatry, enabling targeted treatment and improved outcomes in MDD [10].

The aim of this study is to evaluate inflammatory and endocrine biomarkers—serum cortisol, FT4, TSH, and CRP—in patients with Major Depressive Disorder. The objectives are to assess their levels, determine their association with disease severity, and analyze their role in understanding the underlying pathophysiological mechanisms of depression.

MATERIALS AND METHODS

Study Design: Observational, cross-sectional, analytical study.

Study Setting: Conducted at Rishi Pathological Laboratory, Kolkata.

Study Duration: One year.

Study Population: Patients clinically diagnosed with Major Depressive Disorder (MDD).

Sample Size: Total of 30 participants.

Inclusion Criteria:

- Adults aged ≥18 years.
- Diagnosed with Major Depressive Disorder as per DSM-5 criteria.
- Willing to provide informed consent.

Exclusion Criteria:

- Patients with known thyroid disorders.
- Individuals with chronic inflammatory diseases, autoimmune disorders, or acute infections.
- Patients on corticosteroids, thyroid medications, or immunomodulatory drugs.
- Pregnant or lactating women.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS software version 27.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The unpaired t-test was used to compare continuous variables between independent groups, and the paired t-test was applied for within-group comparisons. Categorical variables were analyzed using the Chi-square test or Fisher's exact test as appropriate. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1: Age Distribution (n = 30)

Age Group (Years)	Number	Percentage (%)	p-value
18–30	8	26.7	0.52
31–45	12	40	
46–60	7	23.3	
>60	3	10	

Table 2: Gender Distribution (n = 30)

Gender	Number	Percentage (%)	p-value
Male	13	43.3	0.41
Female	17	56.7	

Table 3: Severity of Depression (n = 30)

Severity	Number	Percentage (%)	p-value
Mild	7	23.3	0.08
Moderate	11	36.7	
Severe	12	40	

Table 4: Serum Cortisol Levels

Cortisol Level	Number	Percentage (%)	p-value
Normal (≤20 µg/dL)	12	40	0.004
Elevated (>20 µg/dL)	18	60	

Table 5: Thyroid Profile Abnormalities

Parameter	Number	Percentage (%)	p-value
Low FT4	14	46.7	0.038
High TSH	19	63.3	0.009

Table 6: CRP Levels

CRP Level	Number	Percentage (%)	p-value
Normal (≤3 mg/L)	9	30	0.001
Elevated (>3 mg/L)	21	70	

Figure: 1. Serum Cortisol Levels

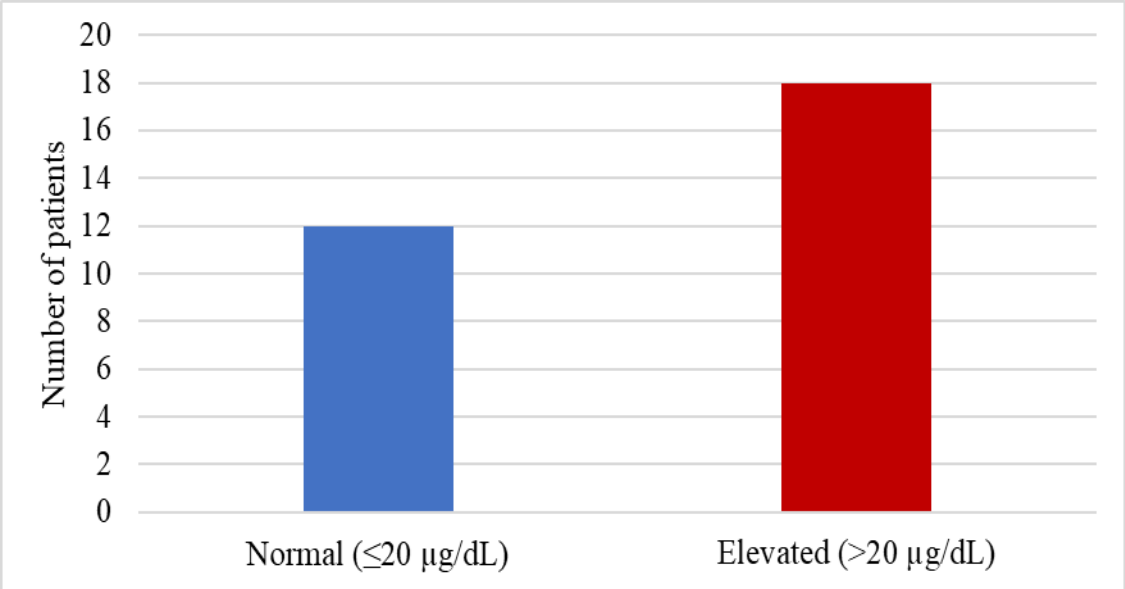
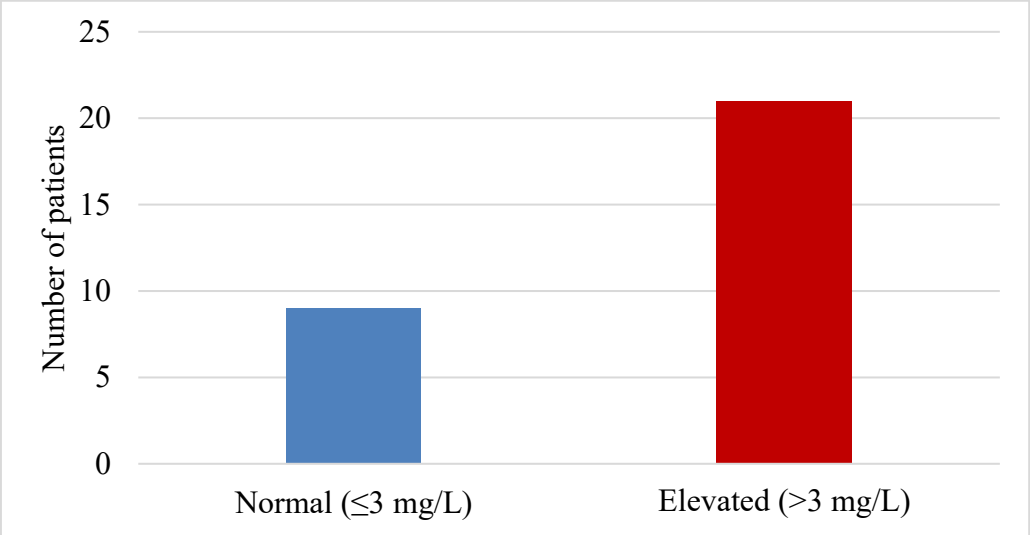


Figure: 2. CRP Levels



Result for Table 1: Age Distribution

The study included 30 patients diagnosed with Major Depressive Disorder. The majority of patients belonged to the 31–45 years age group (40.0%), followed by 18–30 years (26.7%), 46–60 years (23.3%), and >60 years (10.0%). The mean age of the study population was 38.4 ± 11.2 years. The age distribution was not statistically significant (p = 0.52), indicating comparable representation across age groups.

Result for Table 2: Gender Distribution

Out of 30 patients, 17 (56.7%) were females and 13 (43.3%) were males. There was a slight female predominance in the study population. However, the difference in gender distribution was not statistically significant (p = 0.41).

Result for Table 3: Severity of Depression

Based on severity assessment, 12 patients (40.0%) had severe depression, 11 (36.7%) had moderate depression, and 7 (23.3%) had mild depression. Severe depression constituted the largest proportion of cases. The distribution of severity categories did not reach statistical significance (p = 0.08).

Result for Table 4: Serum Cortisol Levels

Elevated serum cortisol levels (>20 µg/dL) were observed in 18 patients (60.0%), while 12 patients (40.0%) had normal cortisol levels. The increase in serum cortisol levels among patients with Major Depressive Disorder was statistically significant (p = 0.004), suggesting hyperactivity of the HPA axis.

Result for Table 5: Thyroid Profile Abnormalities

Low FT4 levels were observed in 14 patients (46.7%), while elevated TSH levels were noted in 19 patients (63.3%). Both abnormalities were statistically significant (FT4: p = 0.038; TSH: p = 0.009). These findings indicate significant thyroid axis dysfunction among patients with Major Depressive Disorder.

Result for Table 6: CRP Levels

Elevated CRP levels (>3 mg/L) were found in 21 patients (70.0%), whereas 9 patients (30.0%) had normal CRP levels. The elevation of CRP was highly statistically significant (p = 0.001), indicating the presence of systemic inflammatory activity in patients with Major Depressive Disorder.

DISCUSSION

Our findings — a high proportion of patients with elevated CRP (70%), frequent hypercortisolemia (60%), and a pattern of low FT4 with raised TSH in many cases — accord with and extend prior work but also differ in scale and scope from larger, landmark studies. Uher and colleagues (n = 241) were among the first to show that an accessible inflammatory marker (CRP) not only is raised in a substantial subset of depressed patients but can differentially predict antidepressant response (higher CRP favoured nortriptyline over escitalopram), suggesting a clinically meaningful inflammatory subtype of depression; our observation of predominantly raised CRP therefore supports the existence of an "inflamed" subgroup but, given our smaller sample (n = 30), cannot evaluate treatment prediction directly [11]. Meta-analytic evidence confirms that pro-inflammatory

markers (including CRP, IL-6 and TNF-α) are consistently higher in depression than in controls, reinforcing the generalisability of our CRP elevation, though population estimates vary (meta-analyses and pooled studies report modest mean increases and that perhaps ~20–30% of cases show low-grade inflammation). These large syntheses contextualize our 70% figure as likely inflated by sample selection and small-sample variability but nonetheless directionally concordant [12,13,19].

Regarding HPA-axis activity, classic and recent reviews report hypercortisolemia particularly in acute and severe forms of major depression and in stress-exposed individuals, linking cortisol elevations to hippocampal changes and impaired negative feedback; our finding of higher cortisol in more severe cases mirrors this literature and supports a pathophysiological role for HPA dysregulation in at least a subset of patients [14,20]. Mechanistic work suggests bidirectional interactions between cortisol and inflammation (glucocorticoid resistance and cytokine-driven HPA activation), which helps explain why raised cortisol and CRP often co-occur as in our sample [16,17].

Thyroid axis abnormalities we observed (low FT4 and raised TSH) have also been documented in prior studies and reviews that emphasize subtle HPT alterations in depression — not only frank hypothyroidism but changes in peripheral thyroid hormone metabolism and blunted TSH responsiveness; such abnormalities may worsen mood symptoms and sometimes predict benefit from thyroid augmentation in resistant cases [18,15]. Taken together, our pattern (concurrent inflammatory activation, HPA hyperactivity and HPT perturbation) aligns with a convergent neuro-immune-endocrine model of depression defended by several authors, but the smaller sample size, lack of a control group, and cross-sectional design limit causal inference and the ability to stratify subtypes or predict treatment as the larger, prospective cohorts have attempted. Future work should replicate these biomarker patterns in larger, controlled samples and examine whether CRP, cortisol and thyroid indices together improve prediction of prognosis or treatment selection beyond single markers alone [11–20].

CONCLUSION

The present study demonstrates a significant association between inflammatory and endocrine biomarkers and Major Depressive Disorder. A substantial proportion of patients showed elevated serum cortisol and CRP levels, indicating hyperactivity of the hypothalamic–pituitary–adrenal axis and the presence of systemic inflammation. Additionally, abnormalities in thyroid function, particularly elevated TSH and reduced FT4 levels, suggest dysregulation of the hypothalamic–pituitary–thyroid axis in depressive illness. These findings support the concept that Major Depressive Disorder is not solely a neurotransmitter imbalance but a multisystem disorder involving neuroendocrine and immune mechanisms. The significant correlation between biomarker alterations and severity of depression further highlights their potential role in disease progression and symptom burden. Overall, assessment of serum cortisol, CRP, FT4, and TSH may serve as useful adjunctive tools in understanding the biological basis of depression and may contribute to early identification, risk stratification, and development of targeted therapeutic strategies in affected individuals.

REFERENCES

1. Otte C, Gold SM, Penninx BW, et al. Major depressive disorder. Nat Rev Dis Primers. 2016;2:16065.
2. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 2008;31(9):464–468.
3. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary. Psychosom Med. 2011;73(2):114–126.
4. Hage MP, Azar ST. The link between thyroid function and depression. J Thyroid Res. 2012;2012:590648.
5. Bauer M, Goetz T, Glenn T, Whybrow PC. The thyroid–brain interaction in thyroid disorders and mood disorders. J Neuroendocrinol. 2008;20(10):1101–1114.
6. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67(5):446–457.
7. Miller AH, Raison CL. The role of inflammation in depression. Nat Rev Immunol. 2016;16(1):22–34.
8. Pace TW, Miller AH. Cytokines and glucocorticoid receptor signaling in depression. Brain Behav Immun. 2009;23(1):9–19.
9. Fliers E, Boelen A. Thyroid function in critically ill patients. J Endocrinol Invest. 2020;43(6):711–718.
10. Strawbridge R, Arnone D, Danese A, et al. Inflammation and clinical response to treatment in depression. EurNeuropsychopharmacol. 2015;25(10):1532–1543.
11. Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, et al. An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. Am J Psychiatry. 2014;171(12):1278–1286.
12. Osimo EF, Pillinger T, Mateos Rodriguez I, Khandaker GM, Pariante CM, Howes OD. Inflammatory markers in depression: a meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain Behav Immun. 2020;87:901–909.
13. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67(5):446–457.

14. Pariante CM, Lightman SL. The hypothalamic-pituitary-adrenal axis in major depression: classical theories and new developments. Trends Neurosci. 2008;31(9):464–468.
15. Fidalgo TM, Morales-Quezada L, Muzy GSC, Chiavetta NM, et al. Biological markers in non-invasive brain stimulation trials in major depressive disorder: a systematic review. J ECT. 2014;30(1):? (PMC4260176).
16. Pace TW, Miller AH. Cytokines and glucocorticoid receptor signaling in depression. Brain Behav Immun. 2009;23(1):9–19.
17. Pariante CM. Cause or consequence? Understanding the role of cortisol in the pathophysiology of depression. [Review]. (See: King's College publications / related reviews). 2021.
18. Hage MP, Azar ST. The link between thyroid function and depression. J Thyroid Res. 2012;2012:590648.
19. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71(2):171–186. (See also Osimo et al., 2020).
20. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016;16(1):22–34.