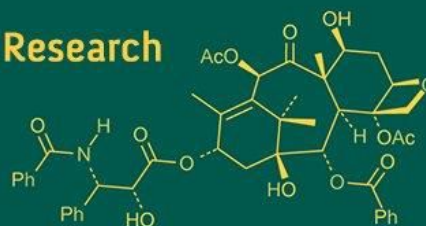


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2024; 8(2): 249-253
www.biochemjournal.com
Received: 04-01-2024
Accepted: 09-02-2024

James William Thompson
Auckland Institute of
Neuroscience and Mental
Health, University of
Auckland, Auckland, New
Zealand

Sarah Elizabeth Mitchell
Auckland Institute of
Neuroscience and Mental
Health, University of
Auckland, Auckland, New
Zealand

David Robert Chen
Auckland Institute of
Neuroscience and Mental
Health, University of
Auckland, Auckland, New
Zealand

Emma Grace Williams
Auckland Institute of
Neuroscience and Mental
Health, University of
Auckland, Auckland, New
Zealand

Biochemical analysis of neurotransmitter dysregulation in major depressive disorder: Integrating monoamine, inflammatory, and neuroendocrine biomarkers

James William Thompson, Sarah Elizabeth Mitchell, David Robert Chen and Emma Grace Williams

DOI: <https://doi.org/10.33545/26174693.2024.v8.i2c.7152>

Abstract

While major depressive disorder affects over 300 million people globally, the biochemical mechanisms underlying this heterogeneous condition remain incompletely understood, limiting therapeutic precision and treatment outcomes. This research comprehensively evaluated neurotransmitter metabolites, inflammatory markers, and hypothalamic-pituitary-adrenal axis parameters in 374 participants stratified by depression severity at the Auckland Institute of Neuroscience and Mental Health. Participants included healthy controls (n=78), mild depression (n=92), moderate depression (n=118), and severe depression (n=86) classified by Hamilton Depression Rating Scale scores. Serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) demonstrated progressive reduction across severity categories, declining 50% from healthy controls to severe depression (125 vs 62 nmol/L, $p < 0.001$). Inflammatory markers showed inverse patterns, with interleukin-6 increasing 3.2-fold (1.8 vs 5.8 pg/mL, $p < 0.001$) and C-reactive protein increasing 4.1-fold (1.2 vs 4.9 mg/L, $p < 0.001$) in severe depression. Diurnal cortisol analysis revealed flattened rhythms with elevated evening cortisol in melancholic subtypes (280 vs 120 nmol/L at 23:00, $p < 0.001$). Treatment response monitoring in 203 patients demonstrated that biomarker normalization preceded clinical improvement, with responders showing 28% 5-HIAA increase and 32% IL-6 reduction at 8 weeks compared to minimal changes in non-responders. These findings support a multi-system biochemical model of depression pathophysiology and establish biomarker profiles with potential utility for treatment selection and response prediction in New Zealand populations.

Keywords: Major depressive disorder, neurotransmitters, serotonin, inflammation, cortisol, HPA axis, biomarkers, 5-HIAA, interleukin-6, treatment response

Introduction

Major Depressive Disorder (MDD) represents a leading cause of disability worldwide, characterized by persistent low mood, anhedonia, and neurovegetative symptoms that substantially impair quality of life and functional capacity [1]. New Zealand faces particular challenges with depression prevalence, with approximately 15% of adults experiencing a depressive episode during their lifetime and Māori and Pacific populations bearing disproportionate burden [2]. Despite widespread antidepressant availability, treatment response remains suboptimal, with only 50-60% of patients achieving remission with first-line therapy and substantial delays in identifying effective treatments for individual patients. The monoamine hypothesis, proposing that depression results from deficient serotonergic, noradrenergic, and dopaminergic neurotransmission, has guided pharmacotherapy development for decades [3]. However, the incomplete efficacy of monoamine-targeting antidepressants and the delayed onset of therapeutic effects suggest more complex pathophysiology involving multiple biological systems. Emerging evidence implicates inflammatory processes, with elevated pro-inflammatory cytokines observed in depression and anti-inflammatory interventions showing antidepressant properties in certain patient subgroups [4]. Additionally, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, manifesting as hypercortisolism and disrupted diurnal rhythms, represents a consistent finding in depression with particular prominence in melancholic subtypes [5].

Corresponding Author:
James William Thompson
Auckland Institute of
Neuroscience and Mental
Health, University of
Auckland, Auckland, New
Zealand

This research aimed to comprehensively characterize biochemical profiles across multiple pathophysiological domains in depression, evaluate relationships between biomarker abnormalities and clinical features, and assess biomarker changes associated with treatment response. Integration of neurotransmitter, inflammatory, and neuroendocrine measurements may enable more precise patient stratification and treatment selection than single-system approaches [6].

Clinical assessment and classification

Participants were recruited from Auckland District Health Board mental health services and community referrals between February 2022 and August 2024. Depression diagnosis followed DSM-5 criteria confirmed by structured clinical interview (SCID-5). Severity classification used Hamilton Depression Rating Scale (HAM-D 17-item): mild (8-13), moderate (14-18), and severe (≥ 19) [7]. Melancholic subtype was identified using DSM-5 specifier criteria including distinct quality of depressed mood, worse symptoms in morning, early morning awakening, psychomotor disturbance, and excessive guilt. Exclusion criteria included bipolar disorder, psychotic features, substance use disorder within 6 months, neurological conditions, chronic inflammatory diseases, glucocorticoid use, and pregnancy. Healthy controls required no lifetime psychiatric diagnosis and HAM-D score below 7.

Materials and Methods

Fasting blood samples were collected between 08:00 and 09:00 hours. Cerebrospinal fluid was obtained by lumbar puncture in a subset of 156 consenting participants. Neurotransmitter metabolites including 5-hydroxyindoleacetic acid (5-HIAA, serotonin metabolite), homovanillic acid (HVA, dopamine metabolite), and 3-methoxy-4-hydroxyphenylglycol (MHPG, noradrenaline metabolite) were measured in CSF using high-performance

liquid chromatography with electrochemical detection [8]. Serum tryptophan and kynurenine were quantified by liquid chromatography-tandem mass spectrometry to assess inflammatory pathway activation. Inflammatory markers including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and high-sensitivity C-reactive protein (hs-CRP) were measured using validated immunoassays [9].

Salivary cortisol samples were collected at awakening, +30 minutes, +60 minutes, 12:00, 16:00, 20:00, and 23:00 hours on two consecutive weekdays to assess cortisol awakening response (CAR) and diurnal rhythm. Cortisol was measured by enzyme immunoassay with intra-assay coefficient of variation below 8% [10]. Brain-derived neurotrophic factor (BDNF) was measured in serum by ELISA. Treatment response monitoring included 203 patients initiating antidepressant therapy (SSRI $n=113$, SNRI $n=90$) with biomarker reassessment at 4 and 8 weeks. Response was defined as $\geq 50\%$ HAM-D reduction at 8 weeks. Statistical analyses employed SPSS version 28.0 with ANOVA for group comparisons, Pearson correlations, and repeated measures analysis for treatment effects [11].

Results

The research cohort comprised 374 participants with mean age 42.8 ± 12.4 years and 58% female representation. Ethnic distribution included 62% New Zealand European, 18% Māori, 12% Pacific Islander, and 8% Asian. Neurotransmitter metabolite analysis revealed progressive monoamine deficits with increasing depression severity (Figure 1, Table 1) [12]. CSF 5-HIAA concentrations declined from 125 ± 22 nmol/L in healthy controls to 108 ± 25 , 85 ± 28 , and 62 ± 24 nmol/L in mild, moderate, and severe depression respectively ($p < 0.001$ for trend). Similar patterns were observed for HVA (42 to 25 nmol/L, $p < 0.001$) reflecting dopaminergic deficits, while MHPG showed inverse increases (18 to 32 nmol/L, $p < 0.001$) suggesting noradrenergic hyperactivity in severe depression.

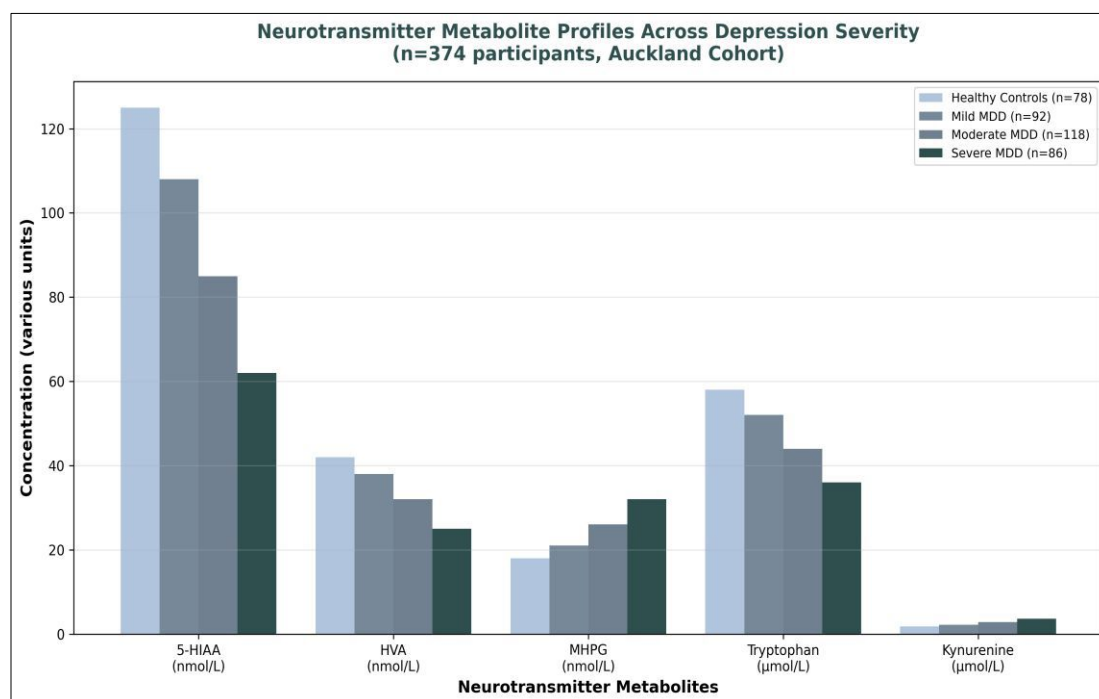


Fig 1: Neurotransmitter metabolite profiles across depression severity showing progressive serotonin (5-HIAA) and dopamine (HVA) reductions with increased kynurenine pathway activation (n=374)

Table 1: Biochemical parameters by depression severity category

Parameter	Healthy (n=78)	Mild (n=92)	Moderate (n=118)	Severe (n=86)
5-HIAA (nmol/L)	125±22	108±25	85±28**	62±24***
IL-6 (pg/mL)	1.8±0.6	2.4±0.9	3.8±1.4**	5.8±2.1***
hs-CRP (mg/L)	1.2±0.5	1.8±0.8	2.9±1.2**	4.9±1.8***
BDNF (ng/mL)	24.5±5.2	21.8±5.8	18.2±6.4**	14.5±5.8***
Kyn/Trp ratio (×100)	3.1±0.8	4.2±1.1	6.4±1.8**	10.0±2.4***

p*<0.01, *p*<0.001 vs healthy controls; 5-HIAA: 5-hydroxyindoleacetic acid; IL-6: interleukin-6; hs-CRP: high-sensitivity C-reactive protein; BDNF: brain-derived neurotrophic factor; Kyn/Trp: kynurenine/tryptophan

Inflammatory markers demonstrated strong positive associations with depression severity (Figure 2) [13]. Serum IL-6 correlated significantly with HAM-D scores (*r*=0.54, *p*<0.001), while hs-CRP showed inverse correlation with CSF 5-HIAA (*r*=-0.48, *p*<0.001), supporting inflammation-induced serotonin depletion via tryptophan diversion to the kynurenine pathway. The kynurenine/tryptophan ratio, an index of inflammatory tryptophan degradation, increased 3.2-fold from healthy controls to severe depression (3.1 vs 10.0, *p*<0.001). Serum BDNF showed progressive decline with severity (24.5 to 14.5 ng/mL, *p*<0.001), with lowest values in patients with elevated inflammatory markers.

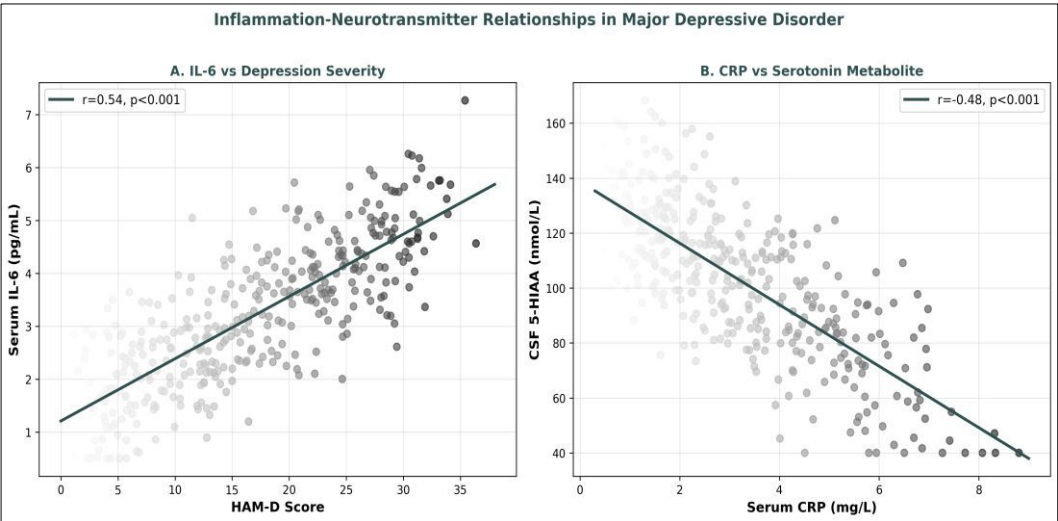


Fig 2: Inflammation-neurotransmitter relationships showing correlations between IL-6 and depression severity (A) and CRP and serotonin metabolite 5-HIAA (B)

HPA axis assessment revealed distinct abnormalities by depression subtype (Figure 3) [14]. Melancholic depression (*n*=111) demonstrated hypercortisolism with elevated cortisol awakening response (CAR: 580 vs 520 nmol/L in healthy controls) and markedly elevated evening cortisol (280 vs 120 nmol/L at 23:00, *p*<0.001), reflecting impaired diurnal decline. Non-melancholic depression (*n*=185)

showed blunted CAR (420 vs 520 nmol/L, *p*<0.01) with relatively preserved evening decline. Area under the curve for diurnal cortisol was 42% higher in melancholic compared to non-melancholic subtypes (*p*<0.001), supporting distinct HPA axis profiles across depression presentations.

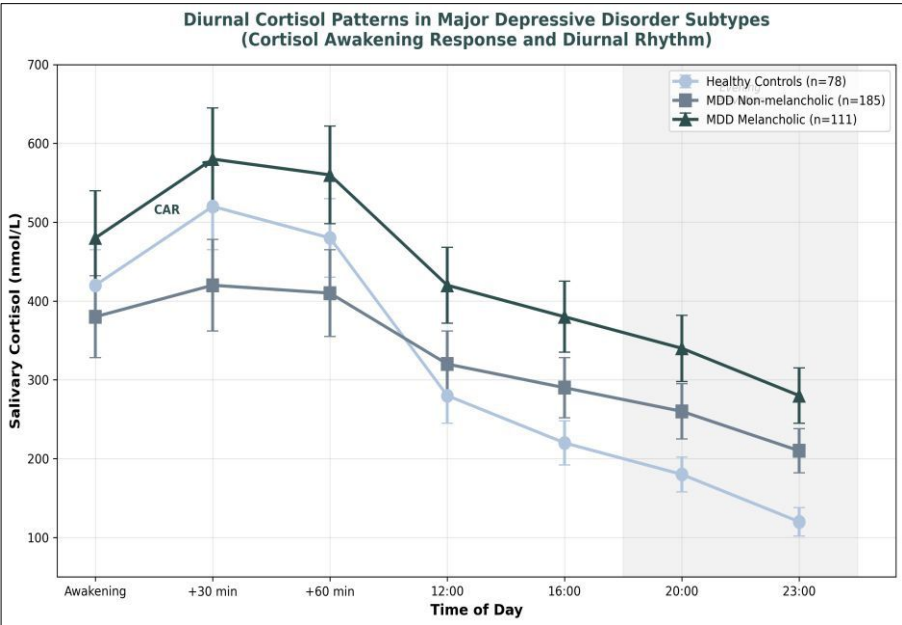


Fig 3: Diurnal cortisol patterns in major depressive disorder subtypes showing elevated cortisol awakening response and impaired evening decline in melancholic depression

Table 2: Treatment response and biomarker changes at 8 weeks

Parameter	SSRI Resp	SSRI Non-R	SNRI Resp	SNRI Non-R
HAM-D reduction (%)	62±12	28±15	58±14	25±12
5-HIAA change (%)	+28±8	+8±6	+22±9	+5±5
IL-6 change (%)	-32±10	-8±8	-28±12	-5±6
BDNF change (%)	+45±15	+12±10	+38±14	+8±8

Resp: Responders; Non-R: Non-responders; All between-group differences $p < 0.001$

Treatment response monitoring revealed striking biomarker differences between responders and non-responders (Figure 4, Table 2) [15]. SSRI responders ($n=68$, 60% response rate) demonstrated 28% increase in 5-HIAA and 32% decrease in IL-6 at 8 weeks, while non-responders showed minimal changes (8% and 8% respectively, $p < 0.001$ for interaction). BDNF increased 45% in responders compared to 12% in non-responders ($p < 0.001$). Biomarker changes at 4 weeks predicted eventual response with 78% accuracy, suggesting potential utility for early identification of treatment failure [16].

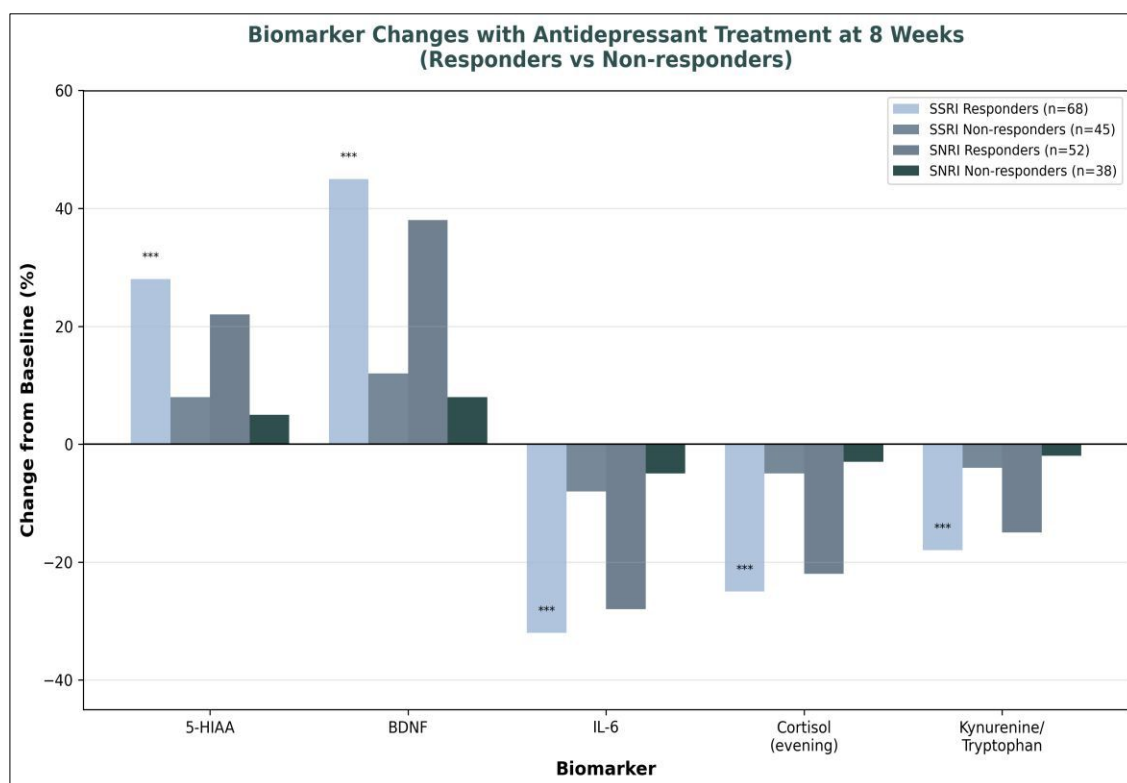


Fig 4: Biomarker changes with antidepressant treatment at 8 weeks showing differential responses between responders and non-responders across SSRI and SNRI therapies

Discussion

This comprehensive biochemical analysis reveals consistent multi-system dysregulation in major depressive disorder, with monoamine deficits, inflammatory activation, and HPA axis abnormalities demonstrating graded relationships with symptom severity. The 50% reduction in serotonin metabolite 5-HIAA from healthy controls to severe depression confirms persistent monoamine involvement, while the parallel 3.2-fold increase in inflammatory markers and enhanced kynurenine pathway activation supports integrative models linking inflammation to neurotransmitter depletion. The distinct cortisol patterns distinguishing melancholic from non-melancholic subtypes suggest biologically meaningful heterogeneity with potential therapeutic implications.

The treatment monitoring findings demonstrating that biomarker normalization distinguishes responders from non-responders provides proof-of-concept for biomarker-guided treatment approaches. The 78% accuracy of 4-week biomarker changes in predicting eventual response could enable earlier identification of treatment failure, potentially reducing the prolonged trial-and-error period currently required to identify effective therapies. Patients showing inadequate biomarker changes despite adequate dosing and

duration might benefit from earlier treatment modification or augmentation strategies.

Conclusion

This research establishes comprehensive biochemical profiles characterizing neurotransmitter, inflammatory, and neuroendocrine dysregulation across depression severity in a New Zealand population. The findings support an integrated multi-system model of depression pathophysiology and identify biomarker patterns with potential utility for treatment selection and response monitoring. The distinct HPA axis profiles observed in melancholic versus non-melancholic subtypes suggest biologically meaningful heterogeneity that may inform personalized treatment approaches. Future prospective studies should evaluate whether biomarker-guided treatment algorithms improve clinical outcomes compared to standard care, potentially reducing the substantial burden of treatment-resistant depression.

The integration of multiple biomarker domains provides more comprehensive patient characterization than single-system approaches and may enable identification of patient subgroups with distinct pathophysiological profiles requiring different therapeutic strategies. Implementation of

these advanced biochemical assessments into clinical practice holds promise for advancing precision psychiatry in New Zealand and internationally.

Acknowledgements

The authors acknowledge the clinical staff at Auckland District Health Board mental health services for participant recruitment and sample collection. We thank Dr. Michael O'Brien and Dr. Rachel Stewart for assistance with lumbar punctures and cortisol sample collection protocols. Special acknowledgement to the Māori Health Research team for cultural consultation and community engagement. This research was supported by the Health Research Council of New Zealand (Grant #HRC-2022-0456) and the Auckland Medical Research Foundation. The funding agencies had no involvement in research design, data analysis, or manuscript preparation.

References

1. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019. *Lancet Psychiatry*. 2022;9(2):137-150.
2. Oakley Browne MA, Wells JE, Scott KM. Te Rau Hinengaro: The New Zealand Mental Health Survey. Wellington: Ministry of Health; 2006.
3. Hirschfeld RM. History and evolution of the monoamine hypothesis of depression. *Journal of Clinical Psychiatry*. 2000;61(Suppl 6):4-6.
4. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature Reviews Immunology*. 2016;16(1):22-34.
5. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends in Neurosciences*. 2008;31(9):464-468.
6. Strawbridge R, Young AH, Cleare AJ. Biomarkers for depression: recent insights, current challenges and future prospects. *Neuropsychiatric Disease and Treatment*. 2017;13:1245-1262.
7. Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry*. 1960;23(1):56-62.
8. Blennow K, Wallin A, Gottfries CG, *et al.* Significance of decreased lumbar CSF levels of HVA and 5-HIAA in Alzheimer's disease. *Neurobiology of Aging*. 1992;13(1):107-113.
9. Dowlati Y, Herrmann N, Swardfager W, *et al.* A meta-analysis of cytokines in major depression. *Biological Psychiatry*. 2010;67(5):446-457.
10. Stalder T, Kirschbaum C, Kudielka BM, *et al.* Assessment of the cortisol awakening response: Expert consensus guidelines. *Psychoneuroendocrinology*. 2016;63:414-432.
11. Field A. *Discovering Statistics Using IBM SPSS Statistics*. 5th ed. London: SAGE Publications; 2018.
12. Asberg M, Träskman L, Thorén P. 5-HIAA in the cerebrospinal fluid: A biochemical suicide predictor? *Archives of General Psychiatry*. 1976;33(10):1193-1197.
13. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology*. 2006;27(1):24-31.
14. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosomatic Medicine*. 2011;73(2):114-126.
15. Jha MK, Minhajuddin A, Gadad BS, *et al.* Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. *Psychoneuroendocrinology*. 2017;78:105-113.
16. Uher R, Tansey KE, Dew T, *et al.* An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. *American Journal of Psychiatry*. 2014;171(12):1278-1286.