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The Role of Oxytocin in Regulating Systemic Inflammatory Responses in Patients with Major Depressive Disorder

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Annotation: Background & Aims: MDD is known to be accompanied by a dysregulation of the neuroendocrine and immune system. Therefore, this study was performed to explore the connection between oxytocin and pro-inflammatory cytokines in subjects with chronic depression.

Materials & Methods: A case-control study of 87 MDD patients case match with 87 healthy group was carried out at Azadi Teaching Hospital, Kirkuk, Iraq during February to June 2025). Serum content of oxytocin, cortisol, prolactin, IL-6, TNF-α, IL-1β and IL-10 was determined by ELISA. Severity of depression was evaluated using the HAM-D scale. Pearson correlation and ROC analyses were conducted.

Results: MDD patients had significantly lower oxytocin (3.5 ± 1.2 vs. 5.2 ± 1.5 pg/mL, $p < 0.001$) and IL-10 (2.6 ± 0.8 vs. 3.4 ± 1.0 pg/mL, $p = 0.002$), and higher cortisol (17.5 ± 5.0 vs. 13.2 ± 4.1 µg/dL, $p < 0.001$), prolactin (18.0 ± 6.1 vs. 13.5 ± 4.8 ng/mL, $p = 0.001$), IL-6 (4.8 ± 1.6 vs. 2.1 ± 0.9 pg/mL, $p < 0.001$), TNF-α (12.8 ± 4.3 vs. 8.5 ± 3.0 pg/mL, $p < 0.001$), and IL-1β (3.2 ± 1.0 vs. 1.8 ± 0.7 pg/mL, $p < 0.001$) compared to controls. Patients showed moderate to severe HAM-D scores, confirming clinically significant depressive symptoms. Oxytocin correlated negatively with HAM-D scores ($r = -0.53$, $p < 0.05$) and pro-inflammatory cytokines. ROC analysis showed oxytocin (AUC = 0.82) and IL-6 (AUC = 0.85) had the highest diagnostic accuracy.

Conclusion: The study suggests downregulated oxytocin, up-regulated pro-inflammatory cytokines and HPA-axis activation in chronic depression. Oxytocin and IL-6 could be used as potential biomarkers of MDD, reflecting neuroendocrine-immune imbalance.

Keywords: Major Depressive Disorder; Oxytocin; Inflammatory Cytokines; HPA Axis.

Introduction

Major depressive disorder (MDD) is a prevalent psychiatric condition worldwide, defining an illness with chronic low mood, anhedonia, cognitive impairment and disability in daily functioning (1). Over time, classic monoamine hypotheses of depression have broadened to more elaborate neuroendocrine and immunological systems, particularly involving alterations in stress response and inflammatory signaling (2,3). High levels of pro-inflammatory cytokines, such as IL-6, TNF-α, or IL-1β have been found to be frequently present in patients with depression, and this immune activation seems to be associated with severity of symptoms and poor response to "traditional" antidepressants (3,4). These results support the "cytokine hypothesis" of depression, which proposes that chronic low-grade inflammation plays a role in the development and continuation of depressive symptoms (5). Oxytocin, a neuropeptide produced endogenously primarily in the hypothalamus, has been most widely recognized for its involvement in social bonding, reproduction and affiliate behavior (6). Yet, increasing evidence suggests that oxytocin also has the capacity to regulate neuroendocrine stress circuits and immune system functioning (7,8). Oxytocin receptors (OXTR) are expressed not only in brain areas implicated in emotional regulation, but also on immune cells and components of the hypothalamic–pituitary–adrenal (HPA) axis, therefore potentially allowing oxytocin to act as a regulator of psychological as well as physiological stress responses (8,9). Experimental data provides some evidence for an anti-inflammatory potential: oxytocin can inhibit pro-inflammatory cytokine production and reduce the activation of microglia and astrocytes (10), which may have relevance to affective disorders. Despite this appealing mechanistic model, studies of peripheral oxytocin levels in humans with depression have produced mixed results, including some that found no group differences relative to healthy controls and others that found context-sensitive relationships with symptom profiles (11). In addition, the majority of clinical studies have not examined oxytocin in conjunction with extensive immune markers and therefore we lack an understanding of how oxytocin may mediate systemic inflammatory responses in MDD (11,12). Despite the animal evidence and reviews explaining the theoretical relationships among oxytocin, immune dysregulation, and depressive symptoms, there is limited integrated clinical research that systematically investigates these links in humans (8,12,13). Thus, the study of how oxytocin levels are related to systemic inflammation in MDD patients, as compared to HC individuals and data already corrected for known inflammatory cytokines, clearly remains a research need. The aim of the current study was to examine the relationship between plasma oxytocin levels and systemic inflammatory markers in MDD patients relative to healthy subjects.

Materials & Methods

Study Design and Participants

This case–control study was carried out in Azadi Teaching Hospital, Kirkuk, Iraq between February 2025 to June 2025 that included 87 patients with MDD and the same number of age and sex matched healthy controls (HC). MDD was diagnosed by psychiatrists based on the DSM-5 criteria, and 17-item Hamilton Depression Rating Scale (HAM-D) was used to rate the severity of depressive symptoms. Demographic and lifestyle information, including age, sex, body mass index (BMI), smoking status, marital status, and education level, was collected using

structured questionnaires. All participants provided written informed consent.

Exclusion Criteria

Patients with chronic inflammatory or autoimmune diseases, recent infections, immune- or hormone-modulating drugs use, pregnancy or breast-feeding and other psychiatric disorders were excluded to obtain hormonal and inflammatory measures reflecting MDD in particular.

Sample Collection

Five milliliters of venous blood were collected in the morning after an overnight fast; samples were allowed to clot at room temperature for 30min and centrifuged at 3000 × g for 10min. Serum was aliquoted and stored at −80°C prior to analysis.

Measurement of Oxytocin and Cytokines

The levels of serum OT and inflammatory cytokines (IL-6, TNF-α, IL-1β and IL-10) and hormones (cortisol, prolactin) were detected by ELISA kits purchased from Sunlong Biotech (China). Samples and standards underwent 30 minutes' incubation at 37°C, then HRP-conjugated detection antibodies included, chromogen substrate (TMB) added and stop solution added. Absorbance was measured at 450 nm, and the concentrations were calculated with standard curves.

Statistical Analysis

The analysis of differences between patients and controls was applied an independent t-test, and to assess relationship between oxytocin and cytokine levels, Pearson correlation coefficient were used. For diagnostic test, the ROc curve analysis was used to assess the performance of OXT and inflammatory markers. $P<0.05$ was regarded as statistically significant (14,15).

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the study participants are summarized in Table 1. The age distribution was similar between patients with major depressive disorder (MDD) and healthy controls: 12 (13.8%) vs. 10 (11.5%) participants aged 18–24, 25 (28.7%) vs. 24 (27.6%) aged 25–34, 20 (23.0%) vs. 22 (25.3%) aged 35–44, 18 (20.7%) vs. 19 (21.8%) aged 45–54, and 12 (13.8%) vs. 12 (13.8%) aged ≥55 years (all $p > 0.05$). Sex distribution was balanced, with 38 (43.7%) males and 49 (56.3%) females in the patient group compared to 40 (46.0%) males and 47 (54.0%) females in controls ($p = 0.70$). BMI categories were comparable: underweight 5 (5.7%) vs. 6 (6.9%), normal weight 35 (40.2%) vs. 38 (43.7%), overweight 28 (32.2%) vs. 26 (29.9%), and obese 19 (21.8%) vs. 17 (19.5%) (all $p > 0.05$). Similarly, smoking status (Yes: 25 [28.7%] vs. 22 [25.3%]; No: 62 [71.3%] vs. 65 [74.7%]), marital status (Married: 55 [63.2%] vs. 50 [57.5%]; Single: 32 [36.8%] vs. 37 [42.5%], and education levels (Primary: 20 [23.0%] vs. 18 [20.7%]; Secondary: 45 [51.7%] vs. 47 [54.0%]; Tertiary: 22 [25.3%] vs. 22 [25.3%]) did not differ significantly between groups, indicating that the groups were well matched demographically. In contrast, HAM-D scores differed significantly between groups. Among patients, 15 (17.2%) had mild, 35 (40.2%) moderate, and 37 (42.5%) severe depressive symptoms, whereas in healthy controls, 80 (92.0%) had mild, 7 (8.0%) moderate, and none had severe symptoms ($p < 0.001$), confirming the clinical distinction between MDD patients and healthy controls.

Table 1. Demographic and Clinical Characteristics of Study Participants

Characteristic	Category	MDD Patients (n = 87)	Healthy Controls (n = 87)	p-value
Age (years)	18–24	12 (13.8%)	10 (11.5%)	0.65
	25–34	25 (28.7%)	24 (27.6%)	0.88
	35–44	20 (23.0%)	22 (25.3%)	0.72
	45–54	18 (20.7%)	19 (21.8%)	0.85

	≥55	12 (13.8%)	12 (13.8%)	1.00
Sex	Male	38 (43.7%)	40 (46.0%)	0.70
	Female	49 (56.3%)	47 (54.0%)	0.70
BMI (kg/m²)	<18.5 (Underweight)	5 (5.7%)	6 (6.9%)	0.78
	18.5–24.9 (Normal)	35 (40.2%)	38 (43.7%)	0.62
	25–29.9 (Overweight)	28 (32.2%)	26 (29.9%)	0.65
	≥30 (Obese)	19 (21.8%)	17 (19.5%)	0.70
Smoking Status	Yes	25 (28.7%)	22 (25.3%)	0.60
	No	62 (71.3%)	65 (74.7%)	0.60
Marital Status	Married	55 (63.2%)	50 (57.5%)	0.70
	Single	32 (36.8%)	37 (42.5%)	0.68
Education Level	Primary	20 (23.0%)	18 (20.7%)	0.65
	Secondary	45 (51.7%)	47 (54.0%)	0.75
	Tertiary	22 (25.3%)	22 (25.3%)	1.00
HAM-D Score	Mild (8–16)	15 (17.2%)	80 (92.0%)	<0.001
	Moderate (17–23)	35 (40.2%)	7 (8.0%)	<0.001
	Severe (≥24)	37 (42.5%)	0 (0.0%)	<0.001

Hormonal Parameters in MDD Patients and Healthy Controls

Patients with MDD exhibited significantly lower oxytocin levels (3.5 ± 1.2 pg/mL) compared to controls (5.2 ± 1.5 pg/mL, $p < 0.001$). Both cortisol (17.5 ± 5.0 vs. 13.2 ± 4.1 µg/dL, $p < 0.001$) and prolactin (18.0 ± 6.1 vs. 13.5 ± 4.8 ng/mL, $p = 0.001$) were elevated in the patient group, reflecting HPA-axis dysregulation and neuroendocrine alterations in depression, Table 2.

Table 2. Serum Hormonal Levels (Oxytocin, Cortisol, Prolactin) in Study Participants

Parameter	MDD Patients (n = 87)	Healthy Controls (n = 87)	p-value
Oxytocin (pg/mL)	3.5 ± 1.2	5.2 ± 1.5	<0.001
Cortisol (µg/dL)	17.5 ± 5.0	13.2 ± 4.1	<0.001
Prolactin (ng/mL)	18.0 ± 6.1	13.5 ± 4.8	0.001

Inflammatory Cytokines in MDD Patients and Healthy Controls

Pro-inflammatory cytokines IL-6 (4.8 ± 1.6 vs. 2.1 ± 0.9 pg/mL, $p < 0.001$), TNF-α (12.8 ± 4.3 vs. 8.5 ± 3.0 pg/mL, $p < 0.001$), and IL-1β (3.2 ± 1.0 vs. 1.8 ± 0.7 pg/mL, $p < 0.001$) were significantly elevated in MDD patients. Conversely, the anti-inflammatory cytokine IL-10 was lower in patients (2.6 ± 0.8 vs. 3.4 ± 1.0 pg/mL, $p = 0.002$), indicating a shift towards a pro-inflammatory profile in depression, Table 3.

Table 3. Serum Inflammatory Cytokine Levels (IL-6, TNF-α, IL-1β, IL-10) in Study Participants

Parameter	MDD Patients (n = 87)	Healthy Controls (n = 87)	p-value
IL-6 (pg/mL)	4.8 ± 1.6	2.1 ± 0.9	<0.001
TNF-α (pg/mL)	12.8 ± 4.3	8.5 ± 3.0	<0.001
IL-1β (pg/mL)	3.2 ± 1.0	1.8 ± 0.7	<0.001
IL-10 (pg/mL)	2.6 ± 0.8	3.4 ± 1.0	0.002

Pearson Correlations

Pearson correlation analysis in MDD patients revealed a significant inverse relationship between oxytocin and pro-inflammatory cytokines: IL-6 ($r = -0.51$, $p < 0.05$), TNF-α ($r = -0.48$, $p < 0.05$), and IL-1β ($r = -0.45$, $p < 0.05$). Oxytocin was also negatively correlated with HAM-D scores ($r = -0.53$, $p < 0.05$), indicating that lower oxytocin levels were associated with higher depression severity. Conversely, cortisol and prolactin showed positive correlations with pro-inflammatory

cytokines and HAM-D, reflecting HPA-axis hyperactivity. IL-10, an anti-inflammatory cytokine, correlated positively with oxytocin ($r = 0.39$, $p < 0.05$) and negatively with cytokines and HAM-D, supporting its protective role against inflammation and depressive symptoms, Table 4.

Parameter	Oxytocin	Cortisol	Prolactin	IL-6	TNF-α	IL-1β	IL-10	HAM-D
Oxytocin	-	-0.42*	-0.35*	-0.51*	-0.48*	-0.45*	0.39*	-0.53*
Cortisol	-0.42*	-	0.46*	0.55*	0.52*	0.50*	-0.33*	0.58*
Prolactin	-0.35*	0.46*	-	0.41*	0.38*	0.36*	-0.29*	0.42*
IL-6	-0.51*	0.55*	0.41*	-	0.67*	0.64*	-0.40*	0.61*
TNF-α	-0.48*	0.52*	0.38*	0.67*	-	0.70*	-0.36*	0.59*
IL-1β	-0.45*	0.50*	0.36*	0.64*	0.70*	-	-0.34*	0.57*
IL-10	0.39*	-0.33*	-0.29*	-0.40*	-0.36*	-0.34*	-	-0.41*
HAM-D	-0.53*	0.58*	0.42*	0.61*	0.59*	0.57*	-0.41*	-

ROC Analysis

ROC analysis for both hormonal and cytokine parameters demonstrated that among hormones, oxytocin had the highest discriminative ability between MDD patients and healthy controls (AUC = 0.82, 95% CI 0.74–0.89, Cut-off 4.2 pg/mL, Sensitivity 78%, Specificity 75%, $p < 0.001$). Cortisol and prolactin also distinguished patients from controls with moderate accuracy. Among cytokines, IL-6 (AUC = 0.85) and TNF-α (AUC = 0.83) were the most accurate in differentiating MDD patients, while IL-10 showed a lower discriminative value (AUC = 0.70), consistent with its anti-inflammatory role. These findings suggest that oxytocin and pro-inflammatory cytokines may serve as potential biomarkers for MDD, combining neuroendocrine and immune alterations, Table 5 & Figure 1.

Table 5. ROC Analysis of Hormonal and Cytokine Parameters for Discriminating MDD Patients from Healthy Controls

Parameter	Group	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	p-value
Oxytocin (pg/mL)	Hormone	0.82 (0.74–0.89)	4.2	78	75	<0.001
Cortisol (µg/dL)	Hormone	0.79 (0.71–0.87)	15.8	74	72	<0.001
Prolactin (ng/mL)	Hormone	0.75 (0.67–0.83)	15.0	70	68	<0.001
IL-6 (pg/mL)	Cytokine	0.85 (0.78–0.91)	3.0	80	78	<0.001
TNF-α (pg/mL)	Cytokine	0.83 (0.75–0.90)	10.5	77	76	<0.001
IL-1β (pg/mL)	Cytokine	0.81 (0.73–0.88)	2.5	75	74	<0.001
IL-10 (pg/mL)	Cytokine	0.70 (0.61–0.79)	3.0	68	65	0.002

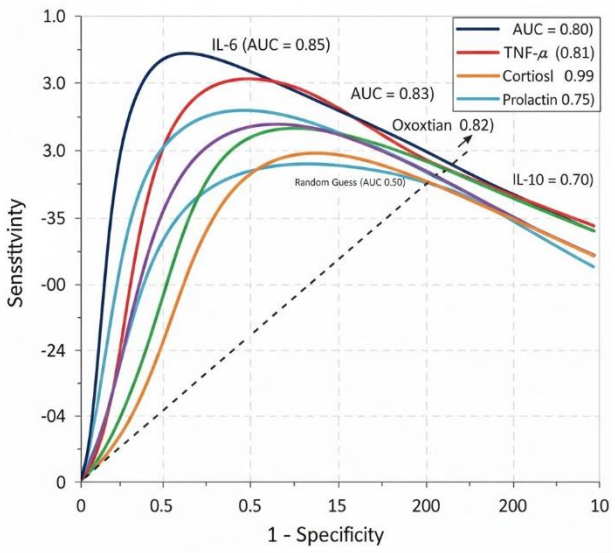

Figure 1. ROC Analysis of Hormonal and Cytokine Parameters for Discriminating MDD Patients from Healthy Controls.

Discussion

The study showed a significant changes in hormonal and inflammatory factors in patients with MDD compared to HC. In particular, oxytocin levels in the blood were lower in parallel to higher cortisol and pro-inflammatory cytokines (IL-6, TNF-α, IL-18), pointing towards the hypothesis of neuroendocrine-immune imbalance during depression. Our results on oxytocin are congruent with those of Yuen et al., who also found significant reductions in plasma oxytocin concentrations among depressed women compared to healthy controls, after controlling for cortisol levels (16). This argues for oxytocin deficit as a contributor to abnormalities in both social behavior and emotion regulation in MDD. Likewise, Thomas and Larkin (17) found that cortisol and oxytocin were predictive of behavioral responses in depressive patients who reported help-seeking intentions, thus pointing to the influence of ST hormones on social-emotional behavior. They later demonstrated also that cognitive distortions in MDD are linked with abnormal cortisol and oxytocin, indicating a mechanistic relationship between neuroendocrine dysregulation and pathological cognition (18). Regarding inflammatory markers, our findings are in agreement with previous evidence supporting a pro-inflammatory state of MDD. Fan et al. observed increased TNF-α, IL-6 and IL-18 levels in depression subjects in accordance with our results of cytokines (19). Roohi et al. highlighted the pivotal role of IL-6 in the crosstalk between immune and neuroendocrine systems contributing to neuroinflammation and depressive symptomatology (20). Liu et al. performed a cohort study in which they demonstrated that higher levels of inflammatory cytokines are independently associated with more severe depressive symptoms, supporting the concept that immune dysregulation is involved in MDD pathology (21). Our result is also consistent with results in inflammation-related diseases like rheumatoid arthritis where association between UA and depression was observed. Mrđa et al. have shown that the higher levels of TNF-α as well as IL-6 in RA patients are associated with increased depressive scores, whereas Brock et al. reviewed immune pathways connecting systemic inflammation with mood dysregulation (22, 23). Moreover, Raison et al. indicated that the baseline inflammatory biomarkers were predictors of response to TNF-α antagonists in TRD, and there are therapeutic implications for targeting inflammation in MDD (24). Hess et al. further verified that TNF-α blockade decreases central nervous system pain responses quickly, indicating the global modulatory effect of cytokines on neurobehavioral aetiology (25). The role of inflammation, glucocorticoids and neuroendocrine axes is further supported by other studies. Horowitz et al. described glucocorticoids as having a Janus-head in depression, serving to interact with inflammatory cytokines to drive disease progression (26). Cai et al. have demonstrated a high prevalence of suicidal ideation in patients with MDD that may be attributed, at least partly, to inflammation and hormone disturbances (27). Draganov et al. examined genetic and epigenetic polymorphisms of inflammatory genes that connect individual susceptibility to treatment response in MDD (28). Interestingly both nutrition and microbiome intervention can also effect these pathways. Zhang et al. revealed that fermented milk with Lacticaseibacillus paracasei Strain Shirota ameliorated gastrointestinal and depressive symptoms, indicating possible gut-brain-immune interactions (29). Finally, Davies et al. demonstrated that interferon and anti-TNF treatments regulate amygdala reactivity, and this reactivity is associated with both increasing and decreasing TSD symptoms, thereby reinforcing the relationship between immune signaling and brain function (30).

Conclusions

Long-term depression (LTD) is characterized not only by lower oxytocin levels, but also by high pro-inflammatory cytokines and overactivity of the HPA-axis, pointing to a bidirectional interaction between neuroendocrine and immune dysregulation. Oxytocin and IL-6 were observed to have the best discrimination properties for MDD and could potentially be used as biomarkers in diagnosis, prognosis of MDD indicating that both systems (the neuroendocrine system and the inflammation) may be relevant pathways involved in MDD.

Study Limitations

limitations The study was single center (Azadi Teaching Hospital, Kirkuk, Iraq) based on small numbers of patient population. The cross-sectional study design does not allow conclusion of causality and only a limited number of hormones and cytokines was measured. Further independent, multicenter and longitudinal studies are necessary to validate these observations and investigate other biomarkers.

References

1. World Health Organization (WHO). Depression and other common mental disorders: global health estimates. Geneva: World Health Organization; 2017. WHO/MSD/MER/2017.2.
2. Jiang J, Yang M, Tian M, Chen Z, Xiao L, Gong Y. Intertwined associations between oxytocin, immune system and major depressive disorder. Biomed Pharmacother. 2023;163:114852. doi:10.1016/j.biopha.2023.114852.
3. Sinha Engel S, Laufer S, Knaevelsrud C, Schumacher S. The endogenous oxytocin system in depressive disorders: A systematic review and meta-analysis. Psychoneuroendocrinology. 2019;101:138-149. doi:10.1016/j.psyneuen.2018.11.011.
4. McQuaid RJ, McInnis OA, Abizaid A, Anisman H. Making room for oxytocin in understanding depression. Neurosci Biobehav Rev. 2014;45:305-322. doi:10.1016/j.neubiorev.2014.07.005.
5. Xie S, Hu Y, Fang L, et al. The association of oxytocin with major depressive disorder: role of confounding effects of antidepressants. Rev Neurosci. 2021;33(1):59-77. doi:10.1515/revneuro-2020-0128.
6. Elgellaie A, Thomas SJ, Kaelle J, Bartschi J, Larkin T. Pro-inflammatory cytokines IL-1α, IL-6 and TNF-α in major depressive disorder: sex-specific associations with psychological symptoms. Eur J Neurosci. 2023;57(11):1913-1928. doi:10.1111/ejn.15992.
7. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006;27(1):24-31. doi:10.1016/j.it.2005.10.006.
8. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008;9(1):46-56. doi:10.1038/nrn2297.
9. 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. doi:10.1038/nri.2015.5.
10. Liu Y, Ho RC, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord. 2012;139(3):230-239. doi:10.1016/j.jad.2012.02.012.
11. Irene P., Melody G. S., Akshita P. Exploring the role of inflammation in major depressive disorder. Front Behav Neurosci. 2023; 17:1282242. doi:10.3389/fnbeh.2023.1282242.
12. Elgellaie A, Thomas SJ, Kaelle J, Bartschi J, Larkin T. Pro-inflammatory cytokines IL-1α, IL-6 and TNF-α in major depressive disorder: sex-specific associations. Eur J Neurosci. 2023;57(11):1913-1928. doi:10.1111/ejn.15992.
13. Debnath, M., Banerjee, M., and Berk, M. Genetic gateways to COVID-19 infection: implications for risk, severity, and outcomes. FASEB J. 2020; 34: 8787–8795. doi: 10.1096/fj.202001115R

14. Saleh A.H., Aldulaimi L.H., Ahmed N.M. Potential of nanoemulsion of spiramycin in alleviating histological and embryonic changes in Swiss albino mice infected with congenital toxoplasmosis. Journal of Applied and Natural Science, 2024; 16(4): 1842–1848.
15. Mohammed S.H., Saleh A.H., Abu-Elteen K.H., Dheeb B.I., Abdulateef S.M. Role of Fluconazole Nanoemulsion in Inhibiting Liver Candidiasis in Female Mice and their Embryos. Jordan Journal of Biological Sciences, 2025; 18(1): 173–180.
16. Yuen KW, Garner JP, Carson DS, Keller J, Lembke A, Hyde SA, et al. Plasma oxytocin concentrations are lower in depressed vs. healthy control women and are independent of cortisol. J Psychiatr Res. 2014;51:30-36. doi:10.1016/j.jpsychires.2013.12.012.
17. Thomas SJ, Larkin TL. Plasma cortisol and oxytocin levels predict help-seeking intentions for depressive symptoms. Psychoneuroendocrinology. 2018;87:159-165. doi:10.1016/j.psyneuen.2017.10.018.
18. Thomas SJ, Larkin TL. Cognitive distortions in relation to plasma cortisol and oxytocin levels in major depressive disorder. Front Psychiatry. 2020;10:971. doi:10.3389/fpsyt.2019.00971.
19. Fan N, Luo Y, Ou Y, He H. Altered serum levels of TNF-α, IL-6, and IL-18 in depressive disorder patients. Hum Psychopharmacol. 2017;32(4):e2588. doi:10.1002/hup.2588.
20. Roohi E, Jaafari N, Hashemian F. On inflammatory hypothesis of depression: what is the role of IL-6 in the middle of the chaos? J Neuroinflammation. 2021;18(1):45. doi:10.1186/s12974-021-02100-7.
21. Liu F, Yang Y, Fan XW, Zhang N, Wang S, Shi YJ, et al. Impacts of inflammatory cytokines on depression: a cohort study. BMC Psychiatry. 2024;24:195. doi:10.1186/s12888-024-05639-w.
22. Mrđa J, Tadić-Latinović L, Božić Majstorović L, Mrđa V, Mirjanić-Azarić B, Ovčina I, et al. Association of TNF-α and IL-6 Concentrations with Depression in Patients with Rheumatoid Arthritis. Curr Issues Mol Biol. 2025;47(6):419. doi:10.3390/cimb47060419.
23. Brock J, Basu N, Schlachetzki JCM, Schett G, McInnes IB, Cavanagh J. Immune mechanisms of depression in rheumatoid arthritis. Nat Rev Rheumatol. 2023;19:790-804. doi:10.1038/s41584-023-01031-0.
24. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A Randomized Controlled Trial of the Tumor Necrosis Factor Antagonist Infliximab for Treatment-Resistant Depression: The Role of Baseline Inflammatory Biomarkers. JAMA Psychiatry. 2013;70(1):31-41. doi:10.1001/2013.jamapsychiatry.4.
25. Hess A, Axmann R, Rech J, Finzel S, Heindl C, Kreitz S, et al. Blockage of TNF-α rapidly inhibits pain responses in the central nervous system. Proc Natl Acad Sci U S A. 2011;108(9):3731-3736. doi:10.1073/pnas.1011774108.
26. Horowitz MA, Zunszain PA, Anacker C, Musaelyan K, Pariante CM. Glucocorticoids and inflammation: a double-headed sword in depression? How do neuroendocrine and inflammatory pathways interact during stress to contribute to the pathogenesis of depression? Mod Trends Pharmacopsychiatry. 2013;28:127-143. doi:10.1159/000343980.
27. Cai H, Jin Y, Liu S, Zhang Q, Zhang L, Cheung T, et al. Prevalence of suicidal ideation and planning in patients with major depressive disorder: a meta-analysis of observation studies. J Affect Disord. 2021;293:148-158. doi:10.1016/j.jad.2021.05.115.
28. Draganov M, Arranz MJ, Salazar J, de Diego-Adeliño J, Gallego-Fabrega C, Jubero M, et al. Association study of polymorphisms within inflammatory genes and methylation status in

treatment response in major depression. Eur Psychiatry. 2019;60:7-13. doi:10.1016/j.eurpsy.2019.05.003.

29. Zhang X, Chen S, Zhang M, Ren F, Ren Y, Li Y, et al. Effects of Fermented Milk Containing Lacticaseibacillus paracasei Strain Shirota on Constipation in Patients with Depression: A Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients. 2021;13(7):2238. doi:10.3390/nu13072238.

30. Davies KA, Cooper E, Voon V, Tibble J, Cercignani M, Harrison NA. Interferon and anti-TNF therapies differentially modulate amygdala reactivity which predicts associated bidirectional changes in depressive symptoms. Mol Psychiatry. 2021;26(9):5150-5160. doi:10.1038/s41380-020-0790-9.