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Serum Thrombospondin- I and Magnesium Levels in Relation to Depression Severity in Male Patients

Running Title: TSP- I and Magnesium in Depression

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ABSTRACT: Background: Major depressive disorder (MDD) is a prevalent mental disorder, affecting both the neurological and metabolic systems. The identification of reliable biomarkers might provide better insight into the pathophysiology of the disease and could help assess its severity. Thrombospondin-1 (TSP-1), a synaptic modulator, and magnesium, as an essential component in neurotransmission, have been implicated in depressive disorders.

Aims: This research aimed to assess serum TSP-1 and magnesium levels in male depressed patients and investigate their relationship to the severity of depression.

Methodology: This case-control study included 130 male participants. Out of the population, the 90 patients with depression were divided into three groups: mild, moderate, and severe based on clinical examination. 40 healthy controls were also included. Serum TSP-1 levels were analyzed by enzyme-linked immunosorbent assay (ELISA), and magnesium levels were measured by spectrophotometry.

Results: Magnesium levels significantly decreased ($p < 0.001$), whereas serum TSP-1 levels progressively increased with depression severity. Magnesium revealed an inverse relationship with depression severity, while TSP-1 showed a positive association. No significant correlation was observed between TSP-1 and magnesium levels in patients with MDD. BMI was positively associated with TSP-1, whereas no significant association was shown between BMI and magnesium. Conclusions: Magnesium and TSP-1 are significantly associated with the severity of depression and may serve as complementary biomarkers that reflect the neurological and metabolic aspects of the disorder.

INTRODUCTION

Depression is a serious mood disorder that manifests as chronic feelings of sadness, a severe low mood, loss of interest, and impaired cognitive function. Depression significantly affects an individual's biological, psychological, and societal functioning. Deep sadness, hopelessness, grief, emptiness, and despair are all components of depression. Over time, the condition may also be associated with psychomotor dysfunction, altered eating and sleeping habits, trouble focusing, and thoughts of suicide ¹. Depression is becoming more prevalent worldwide. As stated by the World Health Organization (WHO), MDD was ranked as the third leading cause of disease burden in 2018 and is expected to overtake all other causes by 2030 ².

The pathogenesis of depression is a complex, multifactorial mechanism that includes the interactions among various neuroendocrine and immune system functions. Chronic stress is believed to be one of the most important etiological factors in the dysregulation of the HPA axis, or hypothalamic-pituitary-adrenal, which may lead to prolonged cortisol release and impaired negative feedback control. Chronic stimulation of this axis leads to overproduction of cortisol and resistance of the corresponding glucocorticoid receptor, thereby halting the normal negative feedback mechanism. This imbalance maintains a chronically high production of pro-inflammatory cytokines and increased immune function, which promotes neuroinflammation and neuronal dysfunction³. Moreover, growing evidence indicates that the pathophysiology of MDD is fundamentally inflammatory in nature, evidenced by increased peripheral inflammatory markers in depressed individuals. The inflammatory processes can also impact brain function through neurotransmission and alter serotonin, dopamine, and norepinephrine systems that are crucial for mood. In addition, HPA axis hyperactivity has been associated with impaired central serotonin transmission, especially in areas like the prefrontal cortex and the hippocampus, where lower serotonin levels aggravate depressive symptoms ⁴.

Thrombospondin-1 (TSP-1) is a multi-functional extracellular matrix glycoprotein predominantly secreted by astrocytes in the central nervous system that plays an important role in synaptogenesis and neural connections. Astrocytic TSP-1 promotes excitatory synapse formation and maturation, thereby facilitating the stability and plasticity of brain circuits. It is a critical regulator of synapse formation. Besides its involvement in synaptogenesis, TSP-1 is involved in a variety of biological processes, including angiogenesis, immune response, and neuroinflammation, all of which are increasingly being recognized as key players in neuropsychiatric disorders⁵. Recent studies suggest that the effects of TSP-1 on synaptic regulation and astrocyte function may be one major pathway mediating the pathophysiology of depression. Due to its impact on major depressive disorder and astrocyte-released TSP-1 in brain transmission and synaptic signaling, there's a strong relationship between a limited role of astrocytes or impaired function. TSP-1 exerts antidepressant-like activity via modulating dopaminergic signalling pathways, especially the dopamine D2 receptor-related mechanism in the medial prefrontal cortex, according to experimental data. The results demonstrate the potential role of TSP-1 as a bridge between glial activity and mood regulation⁶.

Astrocyte activity has been linked to dysregulation of the pathophysiology of major depressive disorder and suicide, further supporting a role for glial cells in mental illnesses. Astrocytes release thrombospondin-1 (TSP-1), a protein that induces the formation of excitatory synapses and regulates their maturation to promote the retention of emerging circuits. In animal studies, recombinant human TSP-1 has been demonstrated to produce antidepressant-like responses through activation of dopaminergic signalling pathways, in particular dopamine D2 receptors in the medial prefrontal cortex. These findings imply that TSP-1 could provide a brand-new target for the treatment of mental disorders, including depression ⁶. Here, astrocytes secrete the multifunctional extracellular matrix protein thrombospondin-1 and play a role in synaptogenesis and brain transmission. Abnormalities in synapses and astrocytes are linked to mental disorders such as depression. Astrocyte dysfunction causes synaptic alterations, which may be integral to the underlying mechanisms of depression. Thus, it has been proposed that TSP-1 is a possible molecule linking the dysfunction of astrocytes to the mechanisms of depressive disorder⁷.

Magnesium is a key element for many biochemical processes occurring in the human body, such as those regulating mood and brain activity. These are essential for synaptic plasticity, neuronal excitability regulation, and healthy brain activity. Several studies have associated dietary deficiency of magnesium with increased vulnerability to major depression, suggesting it might play a role in the pathogenesis of several mood disorders⁸. Magnesium is involved in neurotransmitter systems (which are important for cognition and emotion). It affects serotonergic, glutamatergic, and dopaminergic pathways, all associated with depression. Specifically, magnesium is a naturally occurring NMDA receptor antagonist that prevents excitotoxicity and excessive neuronal excitation, which contribute to the development of depressive disorder when dysregulated⁹.

An imbalance of the HPA axis has been linked to magnesium deficiency. Chronic stress has been shown to suppress feedback control, increase cortisol generation, and lower magnesium status. This imbalance leads to neural inflammation, diminished synaptic plasticity, and oxidative stress⁸. Additionally, Magnesium helps to regulate the inflammatory pathways involved in depression. A lack of magnesium is linked to overproduction of pro-inflammatory cytokines such as TNF- α and IL-6. This state of inflammation has been firmly connected to depressive disorders and neurochemistry, resulting in an imbalance of neurotransmitters and neuronal dysregulation¹⁰.

Studies also suggest that serum magnesium concentrations are reduced in patients suffering from MDD compared with healthy controls. At the same time, some interventional studies showed that magnesium supplements improved depression symptoms, while results are still disputed. This suggests magnesium is a biomarker for the severity of depression¹¹. The connection between levels of magnesium and the severity of depression suggests that magnesium may have clinical implications in mental disorders. Nevertheless, further investigation is required to elucidate its diagnostic and therapeutic potential despite encouraging findings⁸.

METHODOLOGY:

A case-control study included ninety subjects with depression who were initially recruited and enrolled in Ibn-Rushed Hospital Training, Baghdad, Iraq, during the period between December 2025 and April 2026. Subdivided into three subgroups (mild, moderate, and severe), and forty healthy age-matched controls with no signs or symptoms of depression, aged between 25 and 55 years, were also included. BDI was used as part of the inclusion criteria to evaluate depression status and severity¹². Based on earlier, comparable research looking at biomarkers in depression, the sample size was established. A total of 130 participants were included, which was considered adequate to achieve sufficient statistical power for detecting significant differences between groups. Male participants aged between 25 and 55 years with major depressive disorder and classified according to depression severity were included in the study. To prevent hormonal effects, people with neurological disorders, brain injuries, chronic disorders, substance abuse, and female volunteers were excluded.

Participants were evaluated for the severity of depression using the Beck Depression Inventory (BDI)¹³. Venous blood samples were obtained with standardized procedures, and the serum was separated and stored under optimum conditions before analysis. Serum thrombospondin-1 (TSP-1) levels were assessed by using commercial enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource, USA). Serum magnesium values were determined using a commercial assay kit according to the manufacturer's instructions (Sclavo Diagnostics International S.p.A., Italy). Blood samples were extracted from the cubital vein at 8:00 a.m. after an overnight (12-hour) fast for measurement of serum magnesium and thrombospondin-1 (TSP-1). The blood was mixed with SST, then drawn into the tube through a syringe and subsequently centrifuged for 10 min at 4000 x g after being kept at room temperature for about 20 min. After that, the serum was moved to Eppendorf tubes and kept for further examination at -80°C.

Statistical analyses

The collected data were analyzed using Jamovi statistical software (version 2.7.12). To determine if the distribution of continuous variables was normal, the Shapiro-Wilk test was employed. An independent samples T-test was used to find out the comparison of mean values between groups, and the Chi-square test was used to determine the significance of associations between related categorical variables. To evaluate the homogeneity of variances between two or more groups, Levene's test was performed. When the data for magnesium and thrombospondin type-1 yielded heterogeneity of variances, Welch's ANOVA (Welch's one-way analysis of variance) was used. Post hoc comparisons using the Games-Howell test were executed to identify whether the groups under investigation differed in a way that was statistically significant. To examine the relationships between the studied parameters, Pearson's correlation coefficient was applied as a result of the variables' normal distribution and to assess sensitivity and specificity, utilizing magnesium levels and thrombospondin type-1 to distinguish between patients and healthy controls was assessed using the ROC curve. All statistical tests were deemed statistically significant when the p-value was less than 0.05.

Ethical approval

The study protocol was approved by the Research Ethics Committee / Institutional Review Board (IRB) of the College of Medicine, University of Nahrain (Ref. No. 221/3/2; Date: 10 March 2025). Before enrollment, oral informed permission was

obtained from each participant.

RESULTS:

Comparison of the demographic age distribution between study groups.

This was a case-control study involving 130 patients. Ninety individuals were separated into mild, moderate, and severe groups according to how depressed they were. Forty healthy adults constituted the control group who did not show any signs of depression. The depression and healthy control groups were comparable in mean age; Table 1 shows that the study groups did not differ significantly ($p = 0.991$).

Table 1: Differences between the mean age of the case and the control group.

	Group		N	Mean ± SD	P-value
Age	Case	Mild	30	41.6 ± 9.71	0.991
		Moderate	30	39.5 ± 10.19	
		severe	30	41.1 ± 10.09	
	Control	40	40.5 ± 10.25		
Group comparisons were performed using one-way ANOVA.					

Distribution of Sociodemographic Characteristics and BMI Between Patients with MDD and Healthy Controls

Patients and controls did not significantly differ by occupation ($P = 0.789$) or educational attainment ($P=0.079$). But the marital status was different between patients and controls ($P=0.001$), with a higher proportion of married and divorced individuals observed in the patient group. The BMI differed significantly between patients and controls ($P=0.001$). Table 2 shows that in the depression group, there were more overweight and obese people than in the control group.

Table 2: The demographic and clinical characteristics of subjects

		Control		Cases		P-value
		Count	Row N %	Count	Row N %	
Marital status	Single	11	57.9%	8	42.1%	0.009
	Married	28	28.0%	72	72.0%	
	Divorced	1	9.1%	10	90.9%	
Education	Primary	9	50.0%	9	50.0%	0.079
	Secondary	19	32.8%	39	67.2%	
	University	12	22.2%	42	77.8%	
Occupation	Unemployed	17	32.1%	36	67.9%	0.789
	Employed	23	29.9%	54	70.1%	
BMI	Normal	27	48.2%	29	51.8%	0.001
	Obese	2	10.5%	17	89.5%	
	Overweight	10	18.9%	43	81.1%	
	Underweight	1	50.0%	1	50.0%	

Comparison of biochemical parameters according to depression severity and control groups

Table 3 shows that all measured biochemical parameters (FBS, HbA1c, renal function tests, lipid profile, and liver enzymes) demonstrated no significant differences between the four study groups P-value ≥ 0.05

Table 3: Biochemical marker comparisons between study groups and descriptive statistics

	Group	N	Mean $\pm$ SD	p-value
FBS mg/dL	Control	40	87.30 $\pm$ 6.16	0.962
	Mild	30	87.67 $\pm$ 6.12	
	Moderate	30	86.93 $\pm$ 6.24	
	Severe	30	87.67 $\pm$ 6.12	
HbA1c_percent	Control	40	5.11 $\pm$ 0.26	0.280
	Mild	30	5.18 $\pm$ 0.25	
	Moderate	30	5.23 $\pm$ 0.26	
	Severe	30	5.16 $\pm$ 0.28	
Urea_mg/dL	Control	40	28.23 $\pm$ 4.64	0.052
	Mild	30	27.85 $\pm$ 5.18	
	Moderate	30	26.94 $\pm$ 4.32	
	Severe	30	24.70 $\pm$ 5.74	
Creatinine_mg/dL	Control	40	0.92 $\pm$ 0.17	0.341
	Mild	30	0.89 $\pm$ 0.16	
	Moderate	30	0.91 $\pm$ 0.18	
	Severe	30	0.85 $\pm$ 0.14	
Total_Cholesterol_mg/dL	Control	40	167.28 $\pm$ 15.16	0.201
	Mild	30	172.10 $\pm$ 15.75	
	Moderate	30	163.96 $\pm$ 16.80	
	Severe	30	164.51 $\pm$ 16.17	
Triglycerides_mg/dL	Control	40	109.54 $\pm$ 21.55	0.933
	Mild	30	111.92 $\pm$ 21.98	
	Moderate	30	108.47 $\pm$ 19.63	
	Severe	30	109.21 $\pm$ 22.44	
HDL_mg/dL	Control	40	53.11 $\pm$ 7.39	0.788
	Mild	30	52.99 $\pm$ 6.74	
	Moderate	30	51.59 $\pm$ 6.41	
	Severe	30	53.57 $\pm$ 6.94	
LDL_mg/dL	Control	40	97.53 $\pm$ 13.08	0.799
	Mild	30	94.01 $\pm$ 15.22	
	Moderate	30	95.63 $\pm$ 13.65	
	Severe	30	96.07 $\pm$ 14.76	
VLDL_mg/dL	Control	40	15.70 $\pm$ 3.98	0.996
	Mild	30	15.77 $\pm$ 3.91	
	Moderate	30	15.87 $\pm$ 3.95	
	Severe	30	15.93 $\pm$ 4.12	
AST_U/L	Control	40	23.25 $\pm$ 6.87	0.536
	Mild	30	21.79 $\pm$ 6.38	
	Moderate	30	23.96 $\pm$ 7.10	
	Severe	30	24.04 $\pm$ 6.94	
ALT_U/L	Control	40	23.06 $\pm$ 8.66	0.306
	Mild	30	25.78 $\pm$ 8.67	

ALP_U/L	Moderate	30	27.00 ± 9.32	0.369
	Severe	30	24.32 ± 8.85	
	Control	40	84.66 ± 21.55	
	Mild	30	93.09 ± 22.13	
	Moderate	30	86.69 ± 22.96	
	Severe	30	84.71 ± 17.23	

Evaluation of serum TSP-1 and magnesium in study groups

Table 4 shows differences in parameter levels across study groups based on depression severity. Serum TSP-1 levels increased progressively with increasing depression severity. Conversely, magnesium levels decreased as severity increased. These differences were statistically significant according to the Welch's ANOVA test ($P < 0.001$).

Table 4: Descriptive statistics and Welch's ANOVA results of studied parameters according to disease severity

Parameters	Group	N	Mean ± SD	Median	p-value (Welch ANOVA)
TSP-1 (ng/mL)	Control	40	80.1 ± 16.9	79.4	<0.001
	Mild	30	92.9 ± 22.9	89.2	
	Moderate	30	99.7 ± 22.5	97.95	
	Severe	30	129.3 ± 30.2	134.95	
Magnesium (mg/dL)	Control	40	2.10 ± 0.13	2.09	<0.001
	Mild	30	1.99 ± 0.17	1.98	
	Moderate	30	1.83 ± 0.16	1.81	
	Severe	30	1.54 ± 0.23	1.54	

Group comparisons were performed using Welch's ANOVA.

The graphical representations (Figures 1 and 2) demonstrate a clear separation between study groups for both TSP-1 and magnesium levels.

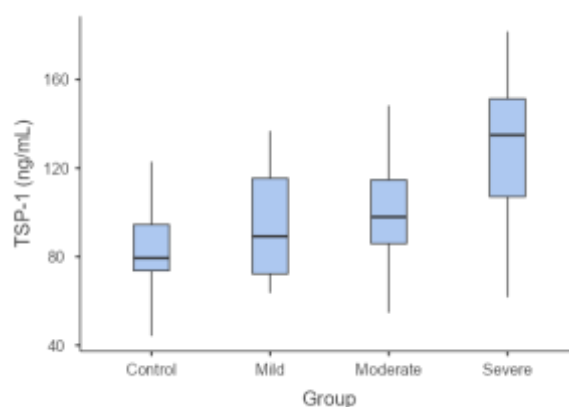


Figure (1): Distribution of TSP-1 levels across the study groups, showing variation with disease severity.

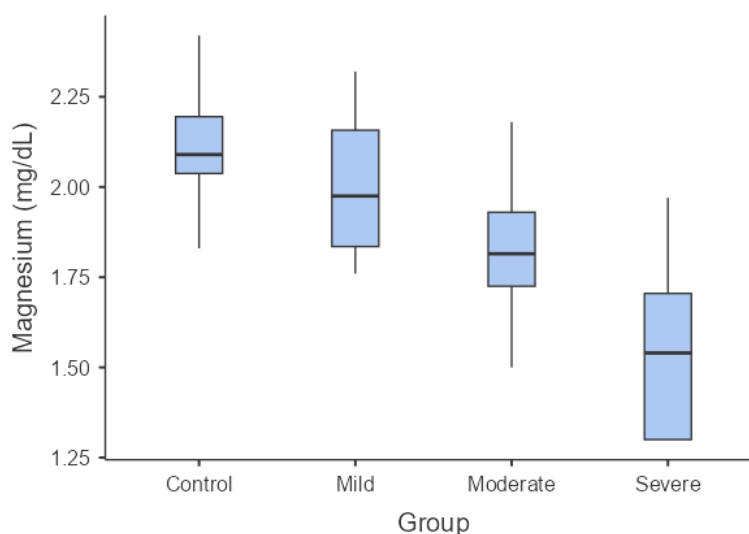


Figure (2): Distribution of Magnesium levels across the study groups, showing variation with depressive severity

Post Hoc Analysis of TSP-1 and magnesium levels among study groups

The values of TSP-1 in the moderate and severe group were significantly greater than in controls, according to post hoc analysis using the Games-Howell test (Table 5). Magnesium levels declined linearly with increasing severity of depression and were considerably lower in patients than in controls.

Table 5: Summary of significant post hoc (Games–Howell) comparisons between study groups

Parameters	Significant comparisons	Direction of difference	p-value
TSP-1 (ng/mL)	Control vs Moderate	Moderate > Control	0.001
	Control vs Severe	Severe > Control	<0.001
	Mild vs Severe	Severe > Mild	<0.001
	Moderate vs Severe	Severe > Moderate	<0.001
Magnesium (mg/dL)	Control vs Mild	Control > Mild	0.018
	Control vs Moderate	Control > Moderate	<0.001
	Control vs Severe	Control > Severe	<0.001
	Mild vs Moderate	Mild > Moderate	0.004
	Mild vs Severe	Mild > Severe	0.020
Group differences were assessed using Welch's ANOVA followed by Games–Howell post hoc test.			

Correlation analysis between TSP-1, magnesium, and body mass index

In Table 6, Pearson correlation analysis demonstrated that TSP-1 and magnesium levels in depressed patients did not statistically significantly correlated ($r = -0.158$, $p = 0.137$), indicating that changes in one biomarker were not directly associated with changes in the other. Regarding BMI, a strong positive correlation was observed with TSP-1 ($r = 0.842$, $p < 0.001$), suggesting that higher body mass index was associated with increased TSP-1 levels.

In contrast, BMI showed a weak and non-significant negative correlation with magnesium levels ($r = -0.175$, $p = 0.099$),

indicating no meaningful association between magnesium status and body mass index in the studied population.

Table 6: Pearson correlations between TSP-1, Magnesium, and BMI of depressed patients

Parameters		TSP-1 (ng/mL)	Magnesium (mg/dL)
TSP-1 (ng/mL)	Pearson's r	—	
	Df	—	
	p-value	—	
Magnesium (mg/dL)	Pearson's r	-0.158	—
	Df	88	—
	p-value	0.137	—
BMI (kg/m ²)	Pearson's r	0.842***	-0.175
	df	88	88
	p-value	<.001	0.099
Note. * p < .05, ** p < .01, *** p < .001			
Pearson correlation was used as all variables showed a normal distribution.			

Diagnostic performance of TSP-1 and Magnesium in differentiating patients with MDD.

In Table 7 and Figure 3, the ROC analysis showed that both TSP-1 and magnesium had good to excellent discriminative ability for patients versus controls (both p<0.001). Magnesium showed better diagnosis ability than TSP-1 (AUC = 0.863) and (AUC = 0.760), respectively. Both biomarkers showed statistically significant diagnostic performance.

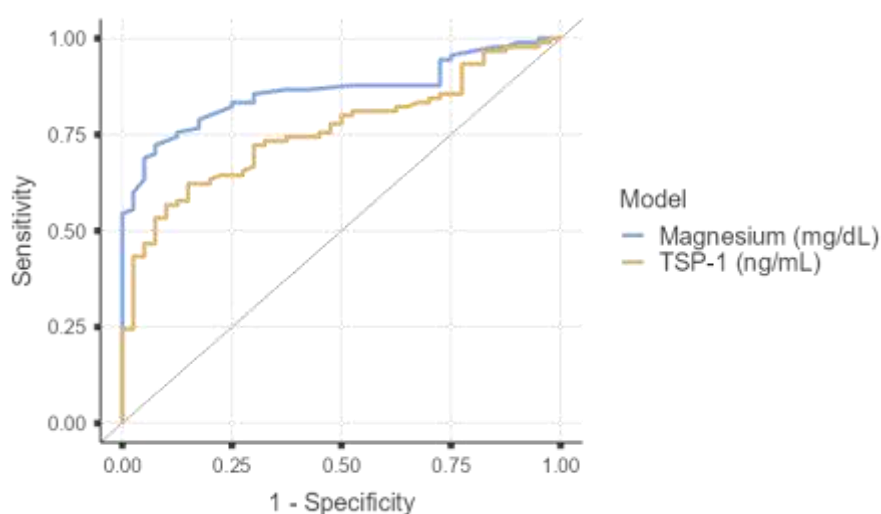


Figure (3): ROC curve shows the sensitivity and specificity of TSP-1 and Magnesium

Table 7. Diagnostic performance of TSP-1 and magnesium for discriminating depressed patients from healthy controls

Parameters	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	p-value
TSP-1 (ng/mL)	0.760 (0.679–0.842)	62.22	85	90.32	50	69.23	<0.001
Magnesium (mg/dL)	0.863 (0.801–0.924)	72.22	92.5	95.59	59.68	78.46	<0.001
AUC: Area under the ROC curve; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value.							

Independent Predictors Associated with Depression Severity.

As shown in Table 8, Binary logistic regression analysis recognized magnesium ($Mg \times 10$) and TSP-1 as significant independent predictors of disease status. Serum magnesium showed a strong inverse association with disease, where each 0.1 mg/dL increase in magnesium was associated with a significant reduction in the odds of depression ($OR = 0.059$, $p < 0.001$).

In contrast, TSP-1 demonstrated a significant positive association with disease status, indicating that higher TSP-1 levels were associated with increased odds ratio of depression ($OR = 1.215$, $p < 0.001$). BMI was not a statistically significant predictor in the model ($p = 0.411$). Overall, the model showed excellent discriminatory performance.

Table 8: Logistic regression model and performance measures for the prediction of disease status

Predictor	β (Estimate)	SE	p-value	OR
Magnesium $\times 10$	-2.823	0.581	<0.001	0.059
TSP-1	0.194	0.040	<0.001	1.215
BMI	0.143	0.174	0.411	1.154
Values are presented as β , SE, OR, and p-value. Magnesium was rescaled ($Mg \times 10$) to express OR per 0.1 mg/dL increase.				

DISCUSSION:

The present study evaluated serum thrombospondin-1 (TSP-1) and magnesium levels in male patients with MDD using the enzyme-linked immunosorbent assay (ELISA) to measure TSP-1 levels, while serum magnesium levels were determined by spectrophotometry.

There was no significant difference in age, employment, or educational level between patients and controls (P -value > 0.05). Married people, however, experienced depression more frequently than people in other marital status categories (P -value = 0.009). These findings were consistent with another study¹⁴.

Our results revealed a distinct pattern in which magnesium levels decrease, but TSP-1 levels gradually increase with the severity of depression. These results suggest the involvement of both neurobiological and metabolic mechanisms in the progression of depressive symptoms. While decreased magnesium levels may suggest compromised neurochemical regulation and heightened physiological stress, a rise in TSP-1 may indicate alterations in synaptic structure and extracellular matrix signaling. These findings support the concept that depression involves not only neurotransmitter problems, but also entails more extensive systemic alterations¹⁵.

A family of oligomeric extracellular matrix proteins called thrombospondins (TSPs) stimulates the establishment of excitatory synapses between cultured neurons. Thrombospondins are present in five isoforms (TSP1–TSP5), and astrocytes in the brain express TSP1–4. TSP1, TSP2, and TSP4 encourage the development of neurites¹⁶. The progressive increase in TSP-1 levels suggests a possible involvement in the pathophysiology of depression, specifically in synaptic remodeling. Since TSP-1 is known to be involved in synaptogenesis, its elevation may reflect synaptic dysfunction or a compensatory mechanism in response to neuronal stress. As depression severity rises, there may be a greater need for synaptic remodeling or repair, which could result in elevated TSP-1 levels. Several studies support the role of synaptic dysfunction in depression, indicating that impairments in neuroplasticity are central to disease progression¹⁷. On the other hand, another study reported a significant decrease in serum TSP-1 levels in female patients with major depressive disorder⁷.

Neuroinflammatory processes may potentially be connected to the increase in TSP-1. It is becoming increasingly acknowledged that depression is an inflammatory disorder in which immune mediators and cytokines affect brain activity. TSP-1 may alter neuronal signaling and symptom intensity by interacting with inflammatory pathways. This finding is consistent with research demonstrating that neuroinflammation is a major factor in depression and may be involved in the severity of symptoms as well as treatment resistance¹⁸. On the other hand, some researchers believe that not all depressed people have inflammation, indicating that disease processes may vary⁴.

Magnesium serves as an essential cofactor in synaptic plasticity and neural signalling. It alters NMDA receptor activation and suppresses excitotoxicity that contributes to mood and emotional balance⁸. Magnesium is necessary to maintain neuronal homeostasis through a number of mechanisms. It functions as a natural NMDA receptor blocker to stop excessive calcium and excitotoxicity¹⁹. Magnesium modulates the expression of brain-derived neurotrophic factor (BDNF), which promotes synaptic plasticity and neuronal survival²⁰.

Our findings of decreased magnesium levels with the severity of depression support the involvement of the magnesium deficit in the pathophysiology of depression. But as it is an important factor in neurotransmission, a shortage of magnesium can result in aberrant neuronal excitability and damage to the regulation of mood. Several studies indicate that magnesium supplementation may be useful in alleviating depressive symptoms¹¹. Nevertheless, earlier investigations have shown that magnesium has been inversely associated with depression symptoms²¹. There is no discernible difference in magnesium levels among depressed and healthy controls, according to some conflicting evidence, which raises the possibility that other variables like nutrition, lifestyle, or comorbidities are at work²².

There is no significant correlation between TSP-1 and magnesium either, indicating that these two biomarkers may not reflect the same molecular mechanism associated with depression. On the other hand, depression is a multi-factorial disorder with various possible reasons, including associated metabolic and neurologic condition². In agreement with previous studies, the present study demonstrated a strong positive correlation between BMI and TSP-1 levels ($r = 0.842$, $p < 0.001$).^{23–25} On the other hand, the current study found only a weak and non-significant negative correlation ($r = -0.175$, $p = 0.099$) between serum magnesium and BMI, despite prior research reporting an inverse relationship. This association has not been consistently observed across all populations and is likely influenced by metabolic and inflammatory mediators²⁶.

ROC analysis revealed diagnostic value for both TSP-1 and magnesium for distinguishing depressed participants from healthy controls. Magnesium, which had more diagnostic performance than TSP-1, which showed moderate discriminative ability, can then be considered promising biomarker candidate, and the finding may be useful when used in combination with other biomarkers as an adjunct. Moreover, TSP-1 and magnesium were independently associated with disease status in binary logistic regression analysis, which may assist in the identification and risk stratification of depression biomarkers. However, their larger and more diverse generalisability is subject to further validation before clinical implementation.

There are some limitations of this study. The nature of our study precludes assessing a potential causal relationship between TSP-1, magnesium levels, and the severity of depression. In addition, because the analysis only included men, its results may not be generalizable to the whole population. Also, the study design with its small sample size may limit generalization. These findings must be improved and verified by further investigations with larger, more diverse populations.

CONCLUSIONS

In brief, the present study indicated that serum magnesium decreased with increased severity of depression while TSP-1 levels

significantly increased. These findings provide insight into metabolic and neurological mechanisms that underlie depression. The results imply that although magnesium may represent more general metabolic changes linked to depression, TSP-1 may be implicated in synaptic remodeling and neuroinflammatory pathways. Together, these two indicators might refine diagnostic assessment and give a more complete picture of the severity of depression.

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Ethical approval

The study protocol was approved by the Research Ethics Committee / Institutional Review Board (IRB) of the College of Medicine, University of Nahrain (Ref. No. 221/3/2; Date: 10 March 2025). Oral informed consent was obtained from all participants before enrollment.

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The authors have no conflicts of interest to disclose.

Authors Contribution:

R.A.J: Conceptualization, Methodology, Investigation, Data Curation, Formal analysis, Writing – Original Draft.

M.I.H: Supervision, Validation, Writing – Review & Editing.

U.K.A.J: Supervision, Writing – Review & Editing.

A.Y.M: Supervision, Writing – Review & Editing.

All authors approved the final manuscript.

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