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Selenium status and tryptophan catabolites as predictive biomarkers of depression in hypothyroid patients

S. Q. Al-Baldawi*, **, H. K. Al-Hakeim***, I. Khémiri*

*University of Tunis El Manar, Tunis, Tunisia
**Al-Esraa University, Baghdad, Iraq
***University of Kufa, Kufa, Iraq

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University of Tunis El Manar, Tunis City, 1124, Tunis.
Tel.: +964-772-740-87-19.
E-mail: rfnk3462@gmail.com

Al-Esraa University, Baghdad, Iraq.

Department of Chemistry, Faculty of Science, University of Kufa , P.O Box 21, Kufa, Najaf Governorate, Iraq.

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Depression is a common comorbidity among patients with hypothyroidism (HT) and is closely associated with alterations in various biological pathways. Among these, selenium (Se), selenoprotein-P (SEPP), and tryptophan catabolites (TRYCATs) have emerged as potential biomarkers. This study aimed to evaluate the predictive role of Se, SEPP, and TRYCATs in identifying depression among hypothyroid patients. A case-control study was conducted on 120 hypothyroid patients, subdivided into two groups: 60 patients with depression (HT+Depression) and 60 without depression (HT only). Additionally, 60 age- and sex-matched healthy individuals served as controls. Serum Se levels were determined using flameless atomic absorption spectrophotometry, while SEPP and TRYCATs, including kynurenic acid (KYNA), 3-hydroxykynurenine (3HK), and quinolinic acid (QA), were quantified via ELISA. The Hamilton Depression Rating Scale (HAM-D) was used to assess depression severity. Statistical analyses included ANOVA, ROC curves, and principal component analysis. Patients in the HT+Depression group exhibited significantly lower levels of SEPP, KYNA, 3HK, and QA/KYNA compared to both the HT-only and control groups. KYNA emerged as the strongest predictor of depression, with a cut-off value of 26.18 nM (Youden's J = 0.634, AUC = 0.89). Principal component analysis demonstrated strong correlations between thyroid biomarkers, TRYCATs, and depression severity. Depression in hypothyroid patients is strongly associated with alterations in Se, SEPP, and TRYCATs. Among these, KYNA shows the highest diagnostic accuracy and may serve as a reliable predictive biomarker for depression in hypothyroidism.

Keywords: hypothyroidism; depression; selenium; selenoprotein-P; tryptophan catabolites; KYNA.

Introduction

The thyroid gland produces important hormones such as thyroxine (T_4) and triiodothyronine (T_3). Hormones govern metabolism, energy generation, and growth and development. Since they affect neurotransmitter production and neuronal integrity, thyroid hormones are crucial for brain development, cognitive function, and mood control) (Hasan et al., 2024; Sabatino & Vassalle, 2025; Vassalle, 2025). A thyroid hormone imbalance may cause hypothyroidism or hyperthyroidism, which can harm physical and mental health. Hypothyroidism (HT), which mostly includes subclinical and overt HT, is a common endocrine condition that is brought on by a reduction in thyroid hormone production and secretion or a lack of the physiologic action of thyroid hormones (Bian, 2025). It was described as having low or normal levels of free thyroxine (FT_4) and high levels of thyroid-stimulating hormone (TSH). This increases energy expenditure, oxygen consumption, respiratory rate, and heat production. The quality of life is negatively impacted after being diagnosed with the HT disease, which could lead to neuropsychiatric disorders, including depressive symptoms (Kamalak et al., 2025). Depression is among the significant symptoms associated with HT (Dehesh et al., 2025). HT could make people more prone to depression, and also severe depression is prevalent in HT (Rehman et al., 2025). Furthermore, the likelihood of developing depressive disorders was strongly correlated with HT (Soheili-Nezhad et al., 2023). While clinical signs are not very suggestive, there is a correlation between HT and depressive disorders that is directly connected to the period of illness (Nicola Marioara et al., 2021). When depression is still in its early stages, individuals may have thyroid abnormalities (Peng et al., 2023).

Depression is associated with alterations in some blood biomarkers. Among these less-studied biomarkers are the tryptophan (TRP) catabolites. Abnormal TRP and serotonin metabolism have been implicated in the pathophysiology of affective disorders (Marx et al., 2021). About 5% of TRP is metabolized into serotonin under the action of aromatic L-amino acid decarboxylase (Li et al., 2024). The remaining 95% of TRP is metabolized to kynurenine (KYN) by the action of two rate-limiting enzymes, tryptophan-2,3-dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO) through the kynurenine pathway (KP) (Tanaka et al., 2021). KYN is further catabolized into kynurenic acid (KYNA) and quinolinic acid (QA), which have neuroprotective and neurotoxic effects, respectively, and the balance between the two metabolites plays an important role in glutamatergic neurotransmission (Martos et al., 2022). Also, hydroxylation of KYN results in 3-hydroxykynurenine (3HK). TRP has been studied as an antimanic drug since the aetiology of depression may be influenced by the decline of serotonin functions (Fellendorf et al., 2021). Because the brain may access the serotonin precursor TRP, biochemical aspects of serotonin shortage in individuals with severe depressive illness are crucial (Torrente et al., 2012). However, a balanced ratio of QA/KYNA may be more successful in preventing depression linked to the NMDA receptor since both acids may serve as agonists (QA) and antagonists (KYNA) for the receptor (Erhardt et al., 2013).

Another parameter that is related to depression is selenium and selenoprotein-P (SEPP), the selenium-containing protein. As a micronutrient, Se affects thyroid pathophysiology by reducing glutathione peroxidase activity, which increases oxidative stress and thyroid tissue destruction (Souza et al., 2025). Selenoprotein-P (SEPP) transports selenium to peripheral tissues, is the main plasma selenoprotein, and has been used as a biomarker of selenium status and intake (Alexander & Olsen, 2023). SEPP sustains selenoenzymes in several tissues and is essential for antioxidative defence and selenium metabolism (Soares et al., 2021). Selenoproteins serve as an efficient defence mechanism against substantial levels of reactive oxygen species (ROS), which thyrocytes continuously produce on their surface to facilitate electron acceptance from oxidative processes. Selenium, as a component of selenoproteins, actively participates in antioxidant, redox, and anti-inflammatory activities (Duntas & Benvenga, 2014). Reduced SEPP levels are associated with elevated levels of depressive symptoms (Birģele et al., 2025). Numerous investigations indicated a substantial inverse correlation between dietary or blood selenium levels and the incidence of depression(Sánchez-Villegas et al.,

2018). Selenium may have a significant role in the therapy of depression owing to its antioxidant, anti-inflammatory, immunomodulatory, and neuroprotective characteristics(Rayman et al., 2012). Nonetheless, selenium supplementation markedly reduced depressed symptoms (Sajjadi et al., 2022). The present study aims to investigate the levels of selenium, SEPP, and TRYCATs biomarkers in HT as predictors of depression in HT patients.

Materials and methods

One hundred and twenty patients with HT were included in the current case-control study. The specimens were collected from Al-Sadr Medical City, Najaf Governorate, Iraq, from September 2024 until November 2024. The study was done per Iraqi and international ethical and privacy regulations. Ethical permission for this study was secured by the Medical Ethics Committee at the University of Kufa, Reference #: MEC-96, per the International Guidelines for Human Research Protection mandated by the Declaration of Helsinki. Informed permission was secured from each participant before their inclusion in the study. The patient's evaluation included a comprehensive medical history to inspect any systemic disorders that may influence the examined parameters. The diagnosis of HT was carried out according to the 10th revision of the International Classification of Diseases and Related Health Problems, Clinical Modification 2024 (ICD-10-CM, Diagnosis Code E03.9). The Hamilton Depression Rating Scale (HAM-D) has 17 symptoms that can be used to calculate the severity of depression. Sixty depressed patients (HT+Depression) who had moderate to severe depression (HAMD>17), as well as sixty HT patients without significant depression called HT only. We deliberately took all Hashimoto's thyroiditis patients in their hypothyroid phase (the progressive phase). The present study excluded any subject with major systemic disease, especially diabetes, viral hepatitis, kidney disease, heart disease, and hypertension. Also, patients with subclinical HT and Hashimoto's thyroiditis in its euthyroid or subclinical hypothyroid phases were excluded. Any subject with a positive serum CRP (CRP > 6 mg/L) was excluded from the study. The test was carried out to eliminate overt inflammation and any unconcealed infection, which causes alteration in the acute phase reactant proteins (Al-Hakeim et al., 2015).

Sixty clinically healthy subjects (29 female and 31 male) were designated as a control group. The ages were comparable to those of the patients (39.9 ± 10.3 years old). The subjects chosen were free from kidney diseases or other systemic, psychiatric, or overt inflammatory disorders.

Five milliliters of fasting blood samples were aspirated from each participant using disposable needles and plastic syringes. The blood was allowed to coagulate for ten to fifteen minutes at room temperature. After that, the blood was centrifuged at 1200^X g for five minutes to separate the serum. Then, sera were transferred to new, disposable Eppendorf tubes and kept at –35 °C in a blood bank deep freeze refrigerator for the working time. The enzyme-linked immunosorbent assay (ELISA) technique was used to estimate 3HK, KYN, KYNA, QA, SEPP, IDO1, and TRP in the sera using ELISA kits purchased from Nanjing Pars Biochem Co., Ltd. (Nanjing, China). All ELISA kits have intra-assay coefficients of variation (CV) below 10%. We applied sample dilutions as required according to the kit's procedures. The electrochemiluminescence immunoassay "ECLIA" was used on Elecsys and Cobas e immunoassay analyzers for the quantitative determination of FT3, FT4, TSH, TPOAb, and TGAb IU/mL in the sera. In the Elecsys FT4 II assay (ROCHE-eLab Doc, Germany) an antigen-specific antibody labelled with tris(2,2'-bipyridyl)ruthenium (II) complex (Ru(bpy)) is used to determine the antigens. The graphite furnace atomic absorption spectrophotometry experiments were conducted using the Shimadzu AA-6300 instrument from Japan for the estimation of serum selenium. As a marker of inflammation, the C-reactive protein (CRP) in human blood was assessed qualitatively and semi-quantitatively using the latex slide test (Spinreact®, Barcelona, Spain).

The sample size of the present case-control study was calculated using G*Power (Version 3.1.9.7). Three groups need 180 individuals to yield a power of 0.85 and an effect size f of 0.25. The distribution of the results was analyzed using the Lilliefors-corrected Kolmogorov-Smirnov test. Results were reported as mean ± standard deviation (SD) for normally distributed variables and median (25–75% interquartile range) for non-normally distributed variables. Fisher's Least Significance (LSD) post-hoc analysis was used for pair-wise comparisons after ANOVA for normally distributed variables. The Kruskal-Wallis (H-test) and Mann-Whitney U-test were used to assess the comparison among non-normally distributed data. The comparison among ordinal variables was examined using contingency tables (χ^2-tests). The natural logarithm transformation of non-normally distributed data was used before the correlation study using Pearson's correlation coefficients. Receiver operating characteristic (ROC) curves evaluated the effectiveness of biomarkers for the diagnosis of depression in HT patients. Principal Component Analysis (PCA) was used to reduce the number of variables of thyroid function tests (PC_Thyroid) and TRYCATs (PC_TRYCATs). The Kaiser-Meyer-Olkin (KMO) test and Bartlett's test of sphericity are crucial PCA statistics for data analysis appropriateness. KMO measures sampling adequacy for factor reduction analysis. The two components show modest sampling adequacy ($0.5 \leq KMO < 0.7$), and significant Bartlett's Test of Sphericity ($P < 0.05$). SPSS 27 (IBM-USA) was used for all statistical analyses (Malik et al., 2023).

Results

Table 1 shows the clinical and demographic characteristics of the HT+Depression, HT, and healthy control groups. Age, weight, height, BMI, sex ratio, smoking, marital status, and residence did not significantly vary across research groups.

Table 1
Demographic and clinical characteristics of HT+ Depression, HT, and healthy control groups

Parameters	Controls	HT	HT+ Depression	F/χ^2	P
Age, year	39.9 ± 10.3	40.9 ± 10.5	41.6 ± 8.1	0.400	0.671
Height, cm	166.4 ± 7.4	166.3 ± 6.8	168.3 ± 6.8	1.586	0.208
Weight, kg	78.4 ± 11.0	77.9 ± 11.0	79.5 ± 8.9	0.345	0.709
BMI, kg/m^2	28.3 ± 3.7	28.1 ± 3.2	28.1 ± 3.0	0.086	0.918
Female/Male	29/31	28/32	27/33	0.134	0.935
Disease duration, year	–	10 (8–12)	12 (8–14)	MWUT	0.229
Smoking (No/Yes)	42/18	41/19	42/18	0.052	0.974
Single/Married	11/49	15/45	18/42	2.226	0.329
Rural/Urban	12/48	15/45	14/46	0.442	0.802
TSH, uIU/mL	2.59 (2.21–3.29)^{B,C}	7.51 (5.72–9.44)^{A}	7.36 (6.04–10.72)^{A}	KWT	<0.001
FT_3, pM	4.30 (3.79–4.64)^{B,C}	3.28 (2.44–4.04)^{A}	3.57 (2.34–4.59)^{A}	KWT	<0.001
FT_4, pM	17.10 ± 2.81^{B,C}	10.13 ± 1.35^{A}	9.75 ± 1.46^{A}	260.118	<0.001
FT_4/FT_3	3.94 (3.37–4.60)^{B,C}	3.03 (2.35–4.01)^{A}	2.86 (2.08–3.99)^{A}	KWT	<0.001
TPOAb, IU/mL	19.0 (10.3–26.0)^{B,C}	239.0 (22.3–365.5)^{A}	261.5 (24.3–478.0)^{A}	KWT	<0.001
TGAb, IU/mL	72.0 (43.0–87.8)^{B,C}	91.5 (45.3–387.5)^{A}	81.5 (56.5–296.8)^{A}	KWT	0.010
L-thyroxin (No/Yes)	–	0/60	0/60	0	1
Corticosteroids (No/Yes)	–	51/9	47/13	0.891	0.345
Inderal (No/Yes)	–	37/23	44/16	1.861	0.172
Hashimoto's thyroiditis (No/Yes)	–	24/36	22/38	0.141	0.707

The comparison between patient groups also shows no significant difference in the disease duration, the ratio of patients with Hashimoto's thyroiditis, and the ratio of patients who took the drugs L-thyroxine, propranolol, and corticosteroids. The results show significant increases in serum TSH, TPOAb, and TGAb in both patient groups compared with the control group. However, there is a significant decrease in FT_3, FT_4, and the FT_4/FT_3 ratio in the patient groups compared with the control group. There is no significant difference between HT and HT+Depression in all the thyroid function tests.

Table 2 shows the results of the measured biomarkers (selenium, SEPP, HAMD, and TRYCATs) in the HT+Depression, HT, and healthy control groups. Serum selenium and TRP levels are significantly lower in the HT+Depression group than in the HT and control groups. While there is no significant difference between the HT and the control group in serum selenium level. Serum SEPP, 3HK, KYNA, and QA/KYNA levels are significantly lower in the HT+Depression group than in the HT and control group. However, there is no discernible difference between the control group and HT. All the research groups showed significant differences in HAMD, QA, and IDO1, with the HT+Depression group having the highest values, followed by the HT and the control groups. Serum KYN, KYNA/KYN, and TRP/KYN do not significantly differ across the research groups.

Table 2
Serum selenium (Se), selenoprotein (SEPP), and tryptophane catabolites (TRYCATs) in patients with depression (HT+Depression), patients without depression (HT), and healthy control groups

Parameters	Controls	HT	HT+Depression	P
Se, ng/mL	136.5 (110.0–161.0) ^{B,C}	79.0 (64.3–99.0) ^{A}	76.5 (59.3–94.8)^{A}	<0.001
SEPP, ng/mL	122.2 (71.5–170.1) ^{C}	141.4 (98.1–175.1) ^{C}	195.2 (151.1–216.9) ^{A,B}	<0.001
TRP, µM	70.7 (33.3–118.8) ^{B,C}	54.3 (33.3–79.2)^{A}	44.0 (29.0–67.2) ^{A}	<0.001
KYN, µM	2.43 (1.33–3.56)	2.02 (1.19–3.10)	1.97 (1.23–2.74)	0.081
3HK, nM	18.3 (11.9–27.7) ^{C}	18.1 (11.5–28.1) ^{C}	34.8 (21.1–76.8) ^{A,B}	<0.001
KYNA, nM	36.6 (24.3–50.2) ^{C}	33.2 (26.6–40.8) ^{C}	23.6 (21.5–25.9) ^{A,B}	<0.001
IDO-1, pg/mL	28.2 (18.6–50.8)^{B,C}	44.1 (23.2–74.7) ^{A,C}	65.7 (36.2–99.2) ^{A,B}	<0.001
QA, nM	288.9 (179.8–473.3)^{B,C}	368.4 (201.4–586.1)^{A,C}	558.0 (325.2–948.6) ^{A,B}	<0.001
QA/KYNA, nM	8.14 (4.98–15.27)^{C}	10.26 (5.79–19.12)^{C}	23.10 (14.99–39.13) ^{A,B}	<0.001
TRP/KYN	33.1 (11.3–66.9)	28.2 (13.6–56.8)	22.2 (13.4–47.9)	0.648
HAMD	5 (4–7) ^{B,C}	7 (6–8)^{A,B}	19 (17–21)^{A,B}	<0.001

There is a significant correlation between total HAMD and 3HK ($r = 0.488$, $P < 0.001$), IDO1 ($r = 0.297$, $P < 0.01$), QA ($r = 0.315$, $P < 0.01$), and SEPP ($rho = 0.322$, $P < 0.01$) in HT patients. While there is a highly significant inverse correlation between HAMD and KYNA ($r = 0.589$, $P < 0.001$). A substantial negative association exists between BMI and IDO1 level ($P = –0.249$, $P < 0.05$). Other biomarkers showed no significant correlation between each other. SEPP has a significant correlation with FT_3 ($r = 0.284$, $P < 0.05$) and the duration of disease ($r = 0.222$, $P < 0.05$), in addition to a significant inverse correlation with the FT4/FT3 ($r = –0.230$, $P < 0.05$). Other thyroid function tests have no significant correlations with the TRYCATs biomarkers.

The results of the multivariate generalized linear model (GLM) analysis of the effect of the diagnosis (presence of disease) and confounders (age, BMI, smoking, and sex) on the measured parameters are presented in Table 3. The results indicated that diagnosis has a significant effect ($F = 34.263$, $P < 0.001$) and can explain 88.5% of the variance of the serum level of the measured biomarkers (partial $\eta^2 = 0.885$). This means that being a patient is the major effector on the changes in serum levels of the measured biomarkers. To elucidate the most affected parameters by diagnosis, the between-subjects effect study was performed on HT and the results are cited in the second part of the table. The presence of disease significantly (all $P < 0.001$) affected the levels of selenium ($F = 127.328$, partial $\eta^2 = 0.423$), KYNA ($F = 59.518$, partial $\eta^2 = 0.255$), QA/KYNA ($F = 57.836$, partial $\eta^2 = 0.249$), IDO1 ($F = 37.199$, partial $\eta^2 = 0.176$), QA ($F = 34.592$, partial $\eta^2 = 0.166$), SEPP ($F = 33.240$, partial $\eta^2 = 0.160$), and 3HK ($F = 31.665$, partial $\eta^2 = 0.154$). The following parameters are not cited in the table because their p-values are less than 0.05: TRP, KYN, TRP/KYN, and KYNA/KYN.

Table 3
Results of multivariate analysis showing the effect of the confounders on the levels of the measured parameters (partial η^2 – effect size)

Tests	Dependent variables	Explanatory variables	F	P	Partial η^2
Multivariate	All biomarkers: Se, KYNA, QA/KYNA, QA, SEPP, 3HK, IDO-1, TRP/KYN, KYNA/KYN, KYN, & TRP.	Diagnosis	34.263	<0.001	0.885
		BMI	1.397	0.096	0.238
		Smoking	1.244	0.194	0.218
		Age	0.905	0.617	0.168
		Sex	0.866	0.675	0.162
Between-subject effects	Diagnosis (HT+Depression/HT/HC)	Selenium	127.328	<0.001	0.423
		KYNA	59.518	<0.001	0.255
		QA/KYNA	57.836	<0.001	0.249
		IDO-1	37.199	<0.001	0.176
		QA	34.592	<0.001	0.166
		SEPP	33.240	<0.001	0.160
		3HK	31.665	<0.001	0.154

The ROC curves for the Se, SEPP, and TRYCATs are plotted in Figure 1, and the diagnostic properties are presented in Table 4. The results show that the increase in SEPP exceeding the cut-off value of 159.97 ng/mL indicates that the patients with HT exhibit a considerable likelihood ($P < 0.001$) of having depression. This is substantiated by the evidence that Youden's J statistic is equal to 0.366. Also, the results indicate that the reduction in serum KYNA below the threshold value of 26.18 nM implies that patients with HT may significantly ($P < 0.001$) exhibit depression, demonstrating a sensitivity and specificity of 81.77% (Youden's J statistic = 0.634). The elevation of the QA/KYNA ratio above the threshold of 14.17 indicates a potential association with depression in hypertensive patients, exhibiting a sensitivity and specificity of 73.3% (Youden's J statistic = 0.466). A 3HK level exceeding the cut-off value of 25.35 nM may significantly predict depression ($P < 0.001$), demonstrating a sensitivity and specificity of 70.0% (Youden's J statistic = 0.400). Serum QA demonstrates a sensitivity and specificity of 63.3% at a cut-off value of 446.29 nM for predicting depression in HT. IDO1 demonstrates a sensitivity and specificity of 56.7% at a cut-off value of 48.61 pg/mL for predicting depression in HT patients. No significant predictability ($P > 0.05$) for depression in HT was observed concerning serum Se, TRP, KYN, TRP/KYN, and KYNA/KYN. Consequently, the diagnostic parameters are absent from the table.

Table 4
Receiver operating characteristic-area under curve (AUC) analysis of the Se and SEPP in prediction of depression in HT patients

Test	Cut-off	Sensitivity, %	Specificity, %	Youden's J statistic	AUC (95% confidence interval)	P-value
KYNA nM*	26.18	81.7	81.7	0.634	0.89 (0.83–0.95)	<0.001
QA/KYNA	14.17	73.3	73.3	0.466	0.80 (0.72–0.88)	<0.001
3HK nM	25.35	70.0	70.0	0.400	0.78 (0.70–0.86)	<0.001
SEPP ng/ml	159.97	68.3	68.3	0.366	0.73 (0.64–0.82)	<0.001
QA nM	446.29	63.3	63.3	0.266	0.70 (0.60–0.79)	<0.001
IDO-1 pg/ml	48.61	56.7	56.7	0.134	0.65 (0.55–0.75)	0.005
TRP/KYN	–	–	–	–	0.47 (0.36–0.57)	0.512
Se ng/ml	–	–	–	–	0.46 (0.35–0.56)	0.407
KYN uM	–	–	–	–	0.45 (0.35–0.55)	0.339
TRP uM	–	–	–	–	0.42 (0.32–0.52)	0.140
KYNA/KYN mM	–	–	–	–	0.40 (0.30–0.50)	0.054

Note: the decrease in this parameter is predictive for depression in HT patients.

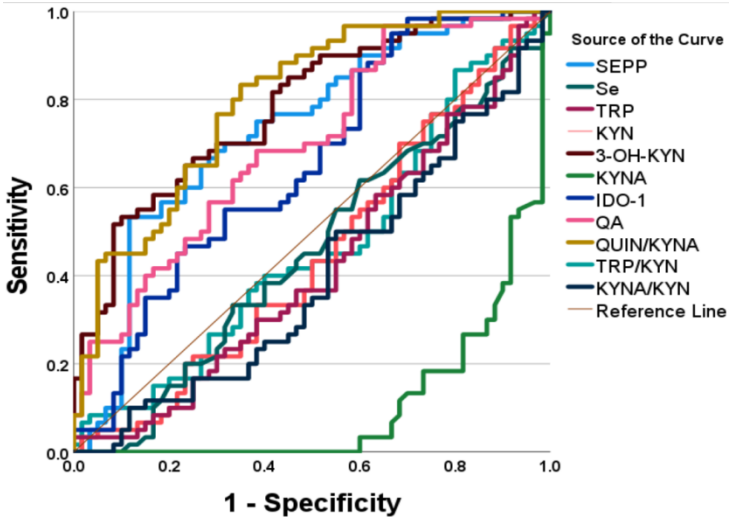

Fig. 1. Receiver operating characteristic curves of the TRYCATs biomarkers in the prediction of depression in HT patients

The scores from the first initial principal component (PC) were derived from the thyroid function tests. This principal component analysis of thyroid function tests (PC_Thyroid) adheres to good standards KMO = 0.641, and a significant Bartlett's test (χ^2 = 66.914, df = 10, P < 0.001)), TRYCATs biomarkers (PC_TRYCATs) (KMO = 0.613, and a significant Bartlett's test (χ^2 = 12.56, df = 15, P < 0.041)). All explained variances were > 50%, and all loadings of the first PC were higher than 0.7. PC_Thyroid was shown to have a significant correlation with SEPP (r = 0.342, P < 0.01), total HAMD (r = 0.544, P < 0.001), and PC_TRYCATs (r = 0.388, P < 0.01). However, there is a significant negative correlation between the PC_Thyroid and selenium (r = –0.601, P < 0.001). Figure 2 shows the correlation between the PC_Thyroid and total HAMD. There is a strong connection between PC_TRYCATs and the following parameters: SEPP (r = 0.373, P < 0.01) and total HAMD (r = 0.598, P < 0.001).

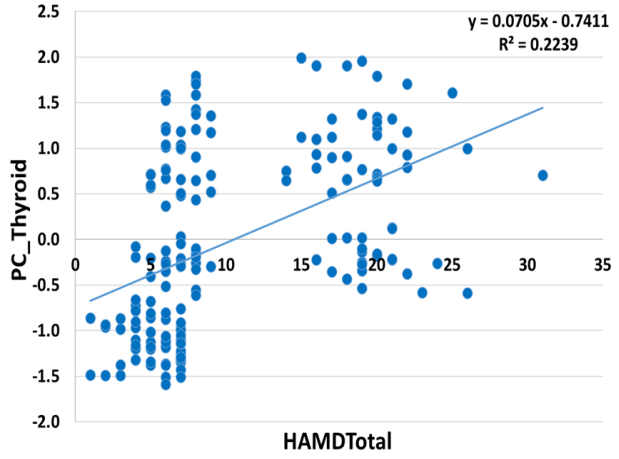

Fig. 2. Correlation between PC_TRYCATs and total HAMD

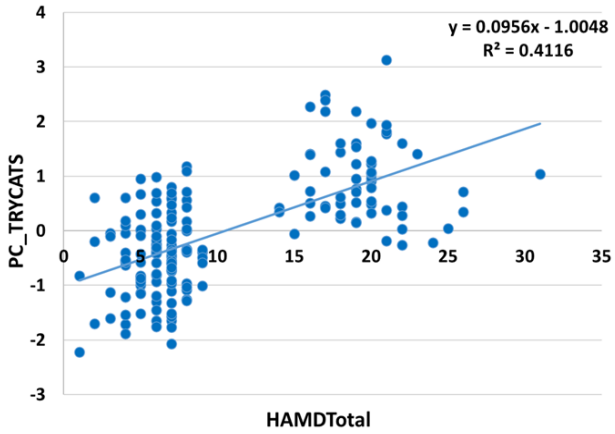

Fig. 3. Correlation between PC_TRYCATs and PC_Thyroid

The PC_TRYCATs have a significant negative connection with selenium (r = 0.355, P < 0.01). Figure 3 shows the correlation between PC_TRYCATs and the total HAMD.

Dsscution

The primary finding of this study is the change in TRYCATs observed in hypothyroid patients with depression (HT+Depression) when compared to non-depressed patients (HT) and control groups. Several factors should be considered when interpreting peripheral TRYCATs data. The conversion of serum TRP to KYN metabolites can reduce the availability of TRP necessary for serotonin synthesis. The reduction of TRP is attributed to enhanced catabolism resulting from the activation of the first and rate-limiting enzyme, IDO, which is stimulated by cell-mediated immune pathways (Maes, 2015). The monoamine-deficit hypothesis posits that a substantial deficiency

of cerebral serotonin is implicated in chronic neuropsychiatric disorders, including mania and depression (Dehhaghi et al., 2019). A significant correlation exists between free or total TRP levels in peripheral blood and the brain, which subsequently influences serotonin synthesis in the central nervous system (Li et al., 2022). Plasma TRP is significantly bound to albumin; thus, alterations in albumin levels may affect TRP availability in the brain. Albumin is a negative acute phase reactant protein that is downregulated during immune-inflammatory responses, including in depression (Maes et al., 1996). The inflammatory response is associated with a reduction in albumin, which may contribute to the decrease in TRP observed in depression. The concentrations of TRYCATs in peripheral circulation account for approximately 60% of the KYN concentrations in the central nervous system (Gál et al., 1980).

Consequently, elevated TRYCATs production and TRP depleteon resulting from peripheral immune-inflammatory processes affect CNS TRYCATs concentrations and production (Schwarcz et al., 2012). The alterations in blood levels of TRYCATs biomarkers may lead to changes in their levels within the central nervous system (CNS). Peripheral blood concentrations of KYN and QA partially influence the CNS concentrations of KYN and QA (Bartoli et al., 2021). The relationship between the coexistence of depression and autoimmune hypothyroidism suggests that the pathomechanism of depression may be linked to alterations in the immune system; it is also plausible that the same immune processes could contribute to both conditions (Kotkowska et al., 2022).

The present study found that selenium and SEPP are also decreased in HT groups and significantly in the HT+Depression group. This indicates that the presence of depression exacerbates the reduction in serum selenium and SEPP levels in HT patients. A significant inverse correlation was observed between selenium intake and depressive symptoms in males (Horng-Tatt, 2019). Serum selenium levels demonstrated a negative correlation with symptoms of depression (Conner et al., 2015) and the likelihood of developing depression (Ibarra et al., 2015). Additionally, research indicates that depressive individuals exhibit reduced selenium levels in comparison to healthy controls (Samad et al., 2019). Furthermore, a significant negative correlation was observed between selenium intake and the risk of depression (Amini et al., 2020). A statistically significant correlation exists between SEPP and symptoms of depression and anxiety, with a tendency observed for students exhibiting these symptoms to have lower selenium levels (Birġele et al., 2025). SEPP functions extend beyond antioxidative enzymes, serving as a crucial component in selenium transportation (Saito et al., 2021). Changes in SEPP levels may play a role in the pathophysiology of depression and anxiety via mechanisms associated with oxidative stress and inflammation, as previously investigated (Barchielli et al., 2022).

The other finding is the various correlations between the depression score and the measured biomarkers. Some researchers showed the same correlations between depression and thyroid tests. It has been found recently that depression was inversely correlated with FT_4, FT_3, and T_3 in both younger and older adults (Ma et al., 2024). Also, depression scores were significantly correlated with the levels of anti-TPOAb and anti-TGAb in patient groups with autoimmune thyroid diseases (Karagun, 2024). Observational studies have linked both HT and depression (Loh et al., 2019).

Only adult females and younger people exhibited a positive connection between TPOAb and depressive symptoms. Depression and thyroid function are significantly correlated; however, this association varies by age group and gender (Ma et al., 2024). Higher levels of depressive symptoms are correlated with lower SEPP levels (Birġele et al., 2025). The previous results reported the effect of selenium in reducing TPOAb levels (Huwiler et al., 2024). A report highlights the potential of SEPP as a biomarker for depression and anxiety, citing its high diagnostic accuracy (Birġele et al., 2025).

The ROC results indicated the predictability of the KYNA, QA/KYNA, 3HK, SEPP, QA, and IDO1 for depression in HT patients. Among them, KYNA shows the highest sensitivity and specificity. Experimental HT is associated with increasing cerebral KYNA levels (Tomczyk & Urbańska, 2020). Thyroid hormones modulate the synthesis of the TRYCATs, suggesting a role in the impairment of CNS function associated with HT (Tomczyk & Urbańska, 2020). Thyroid hormones regulate KYNA levels by two competing pathways: first, by directly inhibiting KATs after translation, and second, by stimulating KATs activity, which is likely transcriptional. The possible impact of T_4 on organic anion transporters and the resultant reduced clearance of KYNA from the brain during HT might explain the lack of association between KATs activity and KYNA level (Tomczyk & Urbańska, 2020).

The principal component analysis of the present study shows interesting findings. Even when the thyroid and TRYCATs biomarkers were reduced into one factor (PC) for each, they still correlated with the HAMD scores as seen in Figures 2 and 3. Researchers have shown that even within the normal range, minor changes in thyroid function may raise the risk of depression in large cohort studies (Kim et al., 2015). Although the strong association between mood and thyroid is undeniable, it is better to understand how hormonal changes impact brain neurotransmission. Thyroid hormones influence the production and action of neurotransmitters such as serotonin and dopamine, key players in mood regulation. In HT, hormone deficiency leads to a decrease in serotonin and dopamine, causing depressive symptoms. Excess hormones in hyperthyroidism accelerate brain activity, impacting these same neurotransmitters and generating anxiety and irritability (Bernardes et al., 2024). In addition to the established comorbidity between HT and depression (Zhou et al., 2024), a recent study by Soheili-Nezhad et al. (2023) indicated that HT was positively linked to the chance of developing depressive disorders (Soheili-Nezhad et al., 2023).

One of the most common mental disorders linked to thyroid disease is depression, in addition to thyroid abnormalities in a high percentage of depressed patients (Peng et al., 2023). Data from a study revealed that more than a quarter of people diagnosed with depression exhibited abnormal thyroid function (Kafle et al., 2020). The findings may be elucidated by the presence of thyroid hormone receptors in many brain areas, including the cerebral cortex, hippocampus, and amygdala, all of which contribute to the aetiology of mental disorders (Williams et al., 2008). A balanced ratio of QA/KYNA can be more effective in avoiding depression concerning the N-methyl-D-aspartate (NMDA) receptor because both the acids can act as an agonist (QA) and antagonist (KYNA) for the receptor (Erhardt et al., 2013). Despite the established knowledge that QA is a neurotoxin capable of over-activating NMDA receptors (Braidy et al., 2009), the precise mechanism remains unclear. Furthermore, research indicates that high QA may elevate ROS production, a significant contributor to neurite deficiencies (Kubicova et al., 2013).

Conclusion

The presence of depression in HT patients is associated with variations in the levels of TRYCATs, Se, and SEPP. The principal components (PC) of thyroid biomarkers (PC_Thyroid) and TRYCATs biomarkers (PC_TRYCATs) showed a significant correlation with the HAMD scores, indicating the presence of three biomarkers for depression in HT patients. These findings can be explained by the effect of these biomarkers on the chemistry of neurotransmitters.

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