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Age-Related Differences in Depression Among Patients with Hypothyroidism: Associations of Irisin, Inflammatory Cytokines, and Immune Cell Ratios

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Abstract:

Objective: To evaluate age-related differences in depressive symptoms among patients with hypothyroidism and to assess their association with circulating irisin, inflammatory markers, immune cell ratios, and thyroid autoantibodies.

Material and Methods: This cross-sectional study included 100 patients with hypothyroidism, stratified into two age groups (25–45 years and 45–65 years). Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9). Serum irisin and interleukin-6 levels were measured using enzyme-linked immunosorbent assay. Systemic inflammation was evaluated using neutrophil–lymphocyte ratio, monocyte–lymphocyte ratio, platelet count, and thyroid autoantibodies. Group comparisons, correlation analyses, and multivariate regression analysis were performed.

Results: Patients aged 45–65 years showed significantly higher depression scores, increased interleukin-6 levels, neutrophil–lymphocyte ratio, monocyte–lymphocyte ratio, platelet counts, and thyroid autoantibody levels, along with significantly lower circulating irisin concentrations compared with younger patients. Irisin demonstrated a significant inverse association with depression severity, whereas inflammatory markers showed positive associations. Irisin and interleukin-6 remained independent predictors of depressive symptoms on multivariate analysis (p-value<0.05).

Conclusion: Age-related immune–metabolic alterations are significantly associated with depressive symptoms in patients with hypothyroidism. Combined assessment of irisin and simple inflammatory markers may help identify individuals at higher risk of depression, particularly in older populations.

Keywords: aging, depression, hypothyroidism, inflammation, irisin

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Introduction

Hypothyroidism is a common endocrine disorder characterized by insufficient production of thyroid hormones, leading to widespread metabolic, neuropsychiatric, and immunological disturbances. Globally, its prevalence continues to rise, particularly among middle-aged and older adults, with women being disproportionately affected. Beyond its classical metabolic manifestations, hypothyroidism is increasingly recognized as a condition with profound neuropsychiatric implications, including depression, cognitive impairment, and reduced quality of life[1,2]. Despite adequate hormonal replacement, a substantial proportion of patients continue to experience depressive symptoms, suggesting the involvement of additional biological mechanisms beyond thyroid hormone deficiency alone.

Growing evidence implicates chronic low-grade inflammation as a central contributor to mood disturbances in hypothyroid individuals. Elevated levels of inflammatory cytokines such as interleukin-6 (IL-6) and C-reactive protein (CRP) have been consistently observed in patients with hypothyroidism and are strongly associated with depressive symptomatology[3,4]. Inflammatory activation can influence neurotransmitter metabolism, hypothalamic–pituitary–adrenal axis function, and neuroplasticity, thereby promoting depressive phenotypes. Moreover, immune dysregulation in hypothyroidism may be amplified by autoimmune mechanisms, particularly in patients with positive thyroid peroxidase or thyroglobulin antibodies, further linking immune activation with neuropsychiatric manifestations[5].

In recent years, irisin has emerged as a novel myokine with significant metabolic and neuroprotective functions. Originally identified as a regulator of energy expenditure and mitochondrial activity, irisin has been shown to exert anti-inflammatory, antioxidant, and neurotrophic effects[6,7]. Experimental and clinical studies suggest that irisin may modulate neurogenesis, synaptic plasticity, and brain-derived neurotrophic factor (BDNF) signaling, pathways that are critically involved in mood regulation and cognitive function[8]. Altered circulating irisin levels have been reported in metabolic disorders, depression, and thyroid dysfunction, indicating a potential integrative role in linking metabolic and neuropsychiatric pathways[9,10].

Age-related changes further complicate this interplay. Aging is associated with increased systemic inflammation ("inflammaging"), altered immune cell profiles, and reduced anabolic signaling, all of which may exacerbate depressive symptoms in vulnerable populations[11]. Biomarkers such as neutrophil–lymphocyte ratio (NLR), monocyte–lymphocyte ratio (MLR), and platelet indices have emerged as simple yet reliable indicators of systemic inflammation and immune dysregulation. Elevated NLR and MLR have been associated with both depression severity and thyroid dysfunction, suggesting their potential utility as integrative biomarkers reflecting immune–neuroendocrine interactions[12,13].

Interleukin-6 plays a central role in linking inflammation with neuropsychiatric symptoms. Elevated IL-6 levels have been consistently reported in major depressive disorders and are known to influence neurotransmitter metabolism, neuroendocrine signaling, and synaptic plasticity[14]. In hypothyroidism, IL-6 elevation may further exacerbate depressive symptoms by amplifying inflammatory cascades and impairing neurocognitive function. Despite this, few studies have comprehensively evaluated IL-6 alongside irisin and immune cell ratios in relation to depression within hypothyroid populations.

Importantly, age-related differences in these associations remain poorly understood. Younger and older hypothyroid patients may exhibit distinct inflammatory and metabolic profiles, potentially influencing susceptibility to depression and response to treatment. Understanding these age-specific patterns is critical for developing personalized therapeutic strategies and improving mental health outcomes in patients with thyroid dysfunction.

Therefore, the present study aims to investigate age-related differences in depressive symptoms among hypothyroid patients by evaluating circulating levels of irisin, IL-6, inflammatory cell ratios (NLR and MLR), and thyroid autoantibodies. By elucidating the interplay between metabolic, inflammatory, and neuropsychiatric factors, this study seeks to provide novel insights into the biological mechanisms underlying depression in hypothyroidism and to identify potential biomarkers for early risk stratification and targeted intervention.

Material and Methods

Study design and setting

This was a hospital-based cross-sectional study conducted in the Department of Biochemistry in collaboration with the Department of Medicine at a tertiary care teaching hospital. The study was carried out during the defined study period after obtaining approval from the Institutional Ethics Committee. All procedures were performed in accordance with the ethical principles outlined in the Declaration of Helsinki.

Study population

A total of 100 adult patients diagnosed with hypothyroidism were enrolled in the study. Participants were categorized into two age-based groups: Group I (25–45 years) and Group II (45–65 years). The diagnosis of hypothyroidism was established based on elevated serum thyroid-stimulating hormone (TSH) levels with or without reduced free thyroxine (FT4), according to standard clinical guidelines.

Sample size calculation

The sample size was calculated based on the primary outcome of differences in depressive symptom scores between the two age groups. Assuming a moderate effect size (Cohen's d=0.5), a two-tailed significance level of 0.05, and a statistical power of 80.0%, a minimum of 45 participants was required in each group. To account for potential incomplete data, the sample size was increased by approximately 10.0%, resulting in a final sample size of 50 participants per group (total n=100).

Inclusion criteria

Patients aged 25–65 years with biochemically confirmed hypothyroidism, either newly diagnosed or receiving stable thyroid hormone replacement therapy, and willing to provide written informed consent were included in the study.

Exclusion criteria

Patients with acute or chronic inflammatory diseases, autoimmune disorders other than autoimmune thyroid disease, known psychiatric illness under pharmacological treatment, chronic liver disease, renal disease, malignancy, or pregnancy were excluded. Individuals receiving steroids, immunosuppressive drugs, or antidepressant medications were also excluded.

Clinical and anthropometric assessment

Detailed demographic and clinical information was recorded using a structured proforma. Anthropometric measurements including height and weight were obtained using standard procedures, and body mass index was calculated. Blood pressure was measured after adequate rest in the seated position.

Assessment of depressive symptoms

Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9), a validated self-report screening tool for depressive symptom severity. A validated English version of the PHQ-9 was used for assessment. Scores were categorized according to established cut-off values to classify the severity of

depressive symptoms. No structured clinical psychiatric interview was performed; therefore, PHQ-9 scores reflect depressive symptom severity rather than a formal clinical diagnosis of major depressive disorder.

Sample collection and laboratory analysis

After an overnight fast of 8–10 hours, venous blood samples were collected under aseptic conditions. Serum and plasma were separated by centrifugation and stored at –80 °C until analysis.

Serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) levels were measured using chemiluminescent immunoassay techniques. Anti-thyroid peroxidase and anti-thyroglobulin antibodies were estimated using enzyme-linked immunosorbent assay.

Serum irisin levels were measured using a commercially available enzyme-linked immunosorbent assay kit according to the manufacturer's instructions. Interleukin-6 (IL-6) levels were estimated using a high-sensitivity enzyme-linked immunosorbent assay.

Complete blood count was analyzed using an automated hematology analyzer. Neutrophil–lymphocyte ratio (NLR) and monocyte–lymphocyte ratio (MLR) were calculated from absolute cell counts. Platelet count was recorded as part of the hematological analysis.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences version 25 (IBM Corp., USA). Normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed variables were expressed as mean±standard deviation, while non-normally distributed variables were expressed as median (interquartile range).

Comparisons between the two age groups were performed using the independent Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using the Chi-square test. Correlations between depressive scores and biochemical parameters were evaluated using Pearson or Spearman correlation coefficients.

Multivariate linear regression analysis was conducted to identify the independent predictors of depressive symptoms after adjusting for age, sex, body mass index, thyroid hormone levels, and inflammatory markers. A p-value<0.05 was considered statistically significant.

Ethical approval

The study protocol was approved by the Institutional Ethics Committee (Approval No. IEC 31/2021). Written informed consent was obtained from all participants prior to enrollment.

Results

Baseline characteristics of the study population

A total of 100 patients with hypothyroidism were included in the analysis, comprising 50 participants aged 25–45 years (Group I) and 50 participants aged 45–65 years (Group II). Baseline demographic and clinical characteristics are presented in Table 1. Sex distribution and body mass index did not differ significantly between the two groups (p-value>0.05). Mean age was significantly higher in Group II compared with Group I (54.6±5.3 years vs. 34.8±5.9 years; p-value<0.001). Serum thyroid-stimulating hormone levels were significantly higher and free thyroxine levels were significantly lower in the older age group (p-value<0.05). Anti-thyroid peroxidase antibody levels were also significantly elevated in Group II, indicating greater autoimmune thyroid activity.

Comparison of inflammatory markers and irisin levels

Comparisons of inflammatory markers and irisin concentrations between the two age groups are shown in Table 2. Patients aged 45–65 years exhibited significantly higher serum interleukin-6 levels compared with younger patients (6.8±1.9 pg/mL vs. 4.1±1.5 pg/mL; p-value<0.001).

Neutrophil–lymphocyte ratio and monocyte–lymphocyte ratio were also significantly increased in Group II (p–value<0.001 and p–value=0.002, respectively). Platelet counts were modestly but significantly higher in the older age group (p–value=0.03). In contrast, circulating irisin concentrations were significantly lower in Group II compared with Group I (4.8±1.2 ng/mL vs. 7.1±1.6 ng/mL; p–value<0.001).

Table 1 Baseline characteristics of study participants

Parameter	Group I (25–45 years)	Group II (45–65 years)	p–value
Age (years)	34.8±5.9	54.6±5.3	<0.001
Male/female (n)	18/32	21/29	>0.050
Body mass index (kg/m^2)	24.6±3.2	25.1±3.6	0.410
Thyroid–stimulating hormone (mIU/L)	6.8±2.1	8.2±2.7	0.003
Free thyroxine (ng/dL)	0.98±0.18	0.86±0.21	0.010
Anti–thyroid peroxidase (IU/mL)	142.6±68.4	198.3±72.5	<0.010

Values are expressed as mean±S.D. unless otherwise indicated
S.D.=standard deviation, TSH=thyroid–stimulating hormone, Anti–TPO=anti–thyroid peroxidase antibody

Table 2 comparison of inflammatory markers and irisin between study groups

Parameter	Group I	Group II	p–value
Irisin (ng/mL)	7.1±1.6	4.8±1.2	<0.001
Interleukin–6 (pg/mL)	4.1±1.5	6.8±1.9	<0.001
Neutrophil–lymphocyte ratio	2.1±0.6	3.2±0.8	<0.001
Monocyte–lymphocyte ratio	0.26±0.07	0.34±0.09	0.002
Platelet count (×10^9/L)	248±42	272±48	0.030

Values are expressed as mean±S.D.
S.D.=standard deviation, IL–6=interleukin–6, NLR=neutrophil–lymphocyte ratio; MLR=monocyte–lymphocyte ratio

Depression severity based on PHQ–9 scores

Depressive symptom severity assessed using the Patient Health Questionnaire–9 differed significantly between age groups (Table 3). Mean PHQ–9 scores were significantly higher in patients aged 45–65 years compared with those aged 25–45 years (12.6±4.1 vs. 7.8±3.2; p–value<0.001). The distribution of depression severity categories showed a higher proportion of moderate to severe depressive symptoms in the older age group. As these categories are descriptive, no inferential statistical test was applied to the percentage distribution.

Table 3 Depression severity based on PHQ–9 scores

Parameter	Group I	Group II
PHQ–9 score (mean±S.D.)	7.8±3.2	12.6±4.1
Minimal–mild depression (%)	48.0%	22.0%
Moderate depression (%)	34.0%	46.0%
Moderately severe–severe depression (%)	18.0%	32.0%

Severity categories are presented as descriptive percentages, no inferential statistical test was applied.
PHQ–9=patient health questionnaire–9, S.D.=standard deviation

Correlation between depression scores and biochemical parameters

Correlation analysis demonstrated a significant inverse association between PHQ–9 scores and serum irisin levels (r=–0.52; p–value<0.001). In contrast, PHQ–9 scores showed significant positive correlations with interleukin–6 (r=0.48; p–value<0.001), neutrophil–lymphocyte ratio (r=0.41; p–value=0.002), monocyte–lymphocyte ratio (r=0.39; p–value=0.004), and anti–thyroid peroxidase antibody levels (r=0.36; p–value=0.006) (Table 4).

Multivariate regression analysis

Multivariate linear regression analysis was performed to identify the independent predictors of depressive symptom severity (Table 5). After adjusting for age, sex, body mass index, and thyroid hormone levels, serum irisin (β=–0.37; p–value=0.002), interleukin–6 (β=0.34; p–value = 0.004), and neutrophil–lymphocyte ratio (β=0.29; p–value=0.01) remained significant independent predictors of PHQ–9 scores. Thyroid–stimulating hormone levels were

not independently associated with depression severity after adjustment (p-value>0.05).

Table 4 Correlation between depression score and biochemical parameters

Variable	r value	p-value
Irisin	−0.52	<0.001
Interleukin-6	0.48	<0.001
Neutrophil–lymphocyte ratio	0.41	0.002
Monocyte–lymphocyte ratio	0.39	0.004
Anti-thyroid peroxidase antibody	0.36	0.006

IL-6=interleukin-6, NLR=neutrophil–lymphocyte ratio, MLR=monocyte–lymphocyte ratio, Anti-TPO=anti-thyroid peroxidase antibody

Discussion

The present study demonstrates a significant association between depressive symptoms and alterations in inflammatory and metabolic biomarkers among patients with hypothyroidism, with notable differences observed across age groups. Our findings indicate that older individuals with hypothyroidism exhibit a higher depressive symptom burden, elevated inflammatory markers, and reduced circulating irisin levels compared to younger counterparts. These findings highlight the complex interplay between immune activation, metabolic dysregulation, and neuropsychiatric manifestations in thyroid dysfunction.

Depression is increasingly recognized as a common neuropsychiatric comorbidity in hypothyroid patients, even among those receiving adequate thyroid hormone replacement. Emerging evidence suggests that inflammatory pathways and immune–endocrine interactions play a pivotal role in mediating depressive symptoms beyond thyroid hormone deficiency alone. In the present study, higher PHQ-9 scores in older individuals were associated with elevated inflammatory markers, supporting the concept of inflammation-driven depression in hypothyroidism[15,16].

The observed elevation of interleukin-6 in older patients aligns with growing evidence that IL-6 is a key mediator linking chronic inflammation to mood disorders. IL-6 has been shown to influence neurotransmitter metabolism, hypothalamic–pituitary–adrenal axis activity, and neuroplasticity, thereby contributing to depressive symptomatology[17,18]. Our findings are consistent with recent reports demonstrating that IL-6 levels correlate positively with depression severity in endocrine and metabolic disorders[19].

Another important finding of the present study is the significant association between inflammatory cell ratios—particularly the neutrophil–lymphocyte ratio and the monocyte–lymphocyte ratio—and depressive symptoms. These ratios have emerged as inexpensive, easily accessible markers of systemic inflammation and immune dysregulation. Recent studies suggest that elevated NLR and MLR are linked to increased depressive severity and poorer neurocognitive outcomes, particularly in chronic

Table 5 multivariate regression analysis for predictors of depression

Variable	β (standardized)	S.E.	p-value
Irisin	−0.37	0.09	0.002
Interleukin-6	0.34	0.11	0.004
Neutrophil–lymphocyte ratio	0.29	0.12	0.010
Age	0.18	0.08	0.04
Thyroid-stimulating hormone	0.11	0.09	>0.05

Multivariate linear regression analysis was adjusted for age, sex, body mass index, thyroid hormone levels, and inflammatory markers. S.E.=standard error; IL-6=interleukin-6, NLR=neutrophil–lymphocyte ratio, TSH=thyroid-stimulating hormone

inflammatory states[21,22]. The present findings extend this evidence to hypothyroid populations, supporting their potential utility as adjunctive biomarkers for neuropsychiatric risk stratification.

Irisin, a myokine implicated in energy homeostasis and neuroplasticity, showed a significant inverse association with depressive symptoms in the current study. Reduced circulating irisin levels in older hypothyroid patients may reflect impaired muscle–brain crosstalk and diminished neuroprotective capacity. Experimental studies have demonstrated that irisin enhances brain-derived neurotrophic factor (BDNF) expression and promotes synaptic plasticity, mechanisms that are crucial for mood regulation[22,23]. Our findings align with recent clinical studies linking reduced irisin levels to depression severity and cognitive dysfunction in metabolic disorders[24].

Importantly, multivariate analysis revealed that irisin, IL-6, and NLR independently predicted depressive symptom severity, even after adjusting for age, sex, and thyroid hormone levels. This underscores the multifactorial nature of depression in hypothyroidism, wherein immune–metabolic dysregulation plays a central role beyond endocrine abnormalities alone. These findings reinforce the concept that targeting inflammation and metabolic pathways may offer therapeutic benefits in managing depression among hypothyroid patients.

The age-related differences observed in this study further highlight the cumulative impact of chronic inflammation and metabolic dysregulation over time. Aging is associated with a state of low-grade inflammation, commonly referred to as "inflammaging," which may amplify susceptibility to mood disorders in the presence of endocrine dysfunction[25]. The higher inflammatory burden and lower irisin levels observed in older participants support this concept, emphasizing the need for age-specific diagnostic and therapeutic strategies.

Despite its strengths, including comprehensive biomarker assessment and age stratification, this study has certain limitations. Its cross-sectional design precludes causal inference, and the lack of longitudinal follow-up limits assessment of temporal relationships. Additionally, several potential confounding factors were not assessed, including physical activity levels, dietary habits, duration and etiology of hypothyroidism, smoking status, and use of anti-inflammatory medications. These variables may influence circulating irisin levels, inflammatory markers, and depressive symptoms. Although patients receiving antidepressant therapy were excluded, subclinical psychological stressors could not be fully accounted for. Furthermore, although an a priori sample size calculation was performed, the relatively modest sample size may limit statistical power for subgroup analyses and generalizability of the findings, highlighting the need for larger, adequately powered multicenter studies.

The present study demonstrates that depressive symptoms in hypothyroid patients are closely associated with increased inflammatory burden and reduced irisin levels, particularly among older individuals. These findings support the role of immune–metabolic dysregulation in the pathophysiology of depression in hypothyroidism and highlight the potential utility of inflammatory and metabolic biomarkers in identifying high-risk patients.

Conclusion

This study demonstrates that depressive symptoms in patients with hypothyroidism are significantly associated with increased inflammatory activity and reduced irisin levels, particularly in older individuals. Elevated IL-6, NLR, and MLR, along with lower circulating irisin, were strongly linked to greater depression severity. These findings suggest that immune–metabolic dysregulation plays a key role in the neuropsychiatric manifestations of hypothyroidism. Assessing inflammatory markers and irisin levels may aid in

identifying patients at a higher risk of depression and support more targeted management strategies. Future longitudinal studies incorporating clinician-administered diagnostic assessments and repeated biomarker measurements are warranted to establish temporal and causal relationships.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of interest

The authors declare that there are no conflicts of interest associated with this study.

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