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RESEARCH ARTICLE
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ASSOCIATION BETWEEN SERUM IRISIN AND LEPTIN LEVELS AND DEPRESSIVE SYMPTOMS IN PATIENTS WITH LONG-STANDING TYPE 2 DIABETES MELLITUS: A CROSS-SECTIONAL STUDY FROM CENTRAL INDIA

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is frequently associated with depression, which negatively affects glycaemic control and quality of life. Recent studies suggest that biomarkers such as irisin and leptin may play a role in the pathophysiology of depression.

Aim: To assess the association between serum irisin and leptin levels and depressive symptoms in patients with T2DM.

Materials and Methods: This was a cross-sectional study conducted over 6 months at the Department of Psychiatry, Index Medical College, Indore. A total of 86 patients with T2DM (≥5 years duration) were recruited. Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) and Hamilton Depression Rating Scale (HAM-D). Patients who screened positive on both scales were labelled as cases; others were classified as controls. Blood samples were analysed for serum irisin and leptin levels using ELISA. Statistical analysis included group comparisons and Spearman correlation.

Results: Out of 86 participants, 29 (33.7%) were classified as having depression. Serum irisin levels were significantly lower, while leptin levels were significantly higher in patients with depression compared to controls. Irisin showed a significant negative correlation with PHQ-9 and HAM-D scores ($r = -0.62$ and -0.59, respectively; $p < 0.001$), while leptin was positively correlated ($r = 0.55$ and 0.51, respectively; $p < 0.001$).

Conclusion: Low serum irisin and high serum leptin levels were strongly associated with depressive symptoms in patients with long-standing T2DM. These biomarkers may serve as useful indicators for early identification of depression in diabetic populations.

Keywords: Type 2 diabetes mellitus, depression, irisin, leptin, PHQ-9, HAM-D, biomarkers, insulin resistance, cross-sectional study

Introduction

Type 2 diabetes mellitus (T2DM) and depression are two common chronic conditions that often coexist[1]. Diabetes is a metabolic disorder marked by chronic hyperglycaemia and insulin resistance, while depression is a mood disorder affecting emotions, cognition, and physical well-being[2]. Studies have shown a bidirectional relationship between the two. Individuals with diabetes have a significantly higher risk of developing depression, and depression may worsen glycaemic control and increase the risk of diabetic complications[3–5].

Various biological mechanisms may explain this link. Chronic systemic inflammation, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, insulin resistance, and oxidative stress may contribute to both diabetes and depressive symptoms[6]. Adipokines and myokines—hormones secreted by adipose tissue and muscle—may play a key role in this interaction[6,7].

Leptin is a hormone secreted by adipocytes that regulates appetite and energy balance[8]. It also acts on the brain and may influence mood, cognition, and the stress response. In obesity and diabetes, leptin resistance is common. Some studies have linked high leptin levels to depressive symptoms. Irisin, a myokine released during physical activity, has been shown to promote neuroplasticity, reduce inflammation, and induce the release of brain-derived neurotrophic factor (BDNF).[9] Low levels of irisin have been reported in both diabetes and depression, suggesting a possible role in their shared pathophysiology.

Although irisin and leptin have been individually linked to depression and diabetes, few studies have explored their combined effect on depressive symptoms in diabetic patients. Most existing research has focused on elderly populations.[10–13] However, depression can affect diabetic patients across all age groups, and younger patients may also suffer significant psychological burden due to the chronic nature of the disease. Understanding the hormonal and biochemical links between T2DM and depression in the general diabetic population may improve early detection and support personalised management.

Depression in patients with type 2 diabetes is underdiagnosed, especially among younger and middle-aged adults. Identifying biological markers linked with depressive symptoms may help in early diagnosis and risk stratification. There is a lack of research examining these associations in the broader diabetic population. This study is designed to fill that gap. By analysing the relationship between serum irisin and leptin levels and depressive symptoms in diabetic patients of all ages, we aim to understand whether these biomarkers can serve as early indicators of depression.

Aim

To evaluate the association between serum irisin and leptin levels and the presence of depressive symptoms in patients with type 2 diabetes mellitus of all age groups who have had diabetes for at least five years.

MATERIAL AND METHODS

- **Study Design:** This study was a cross-sectional observational investigation.
- **Study Setting:** The study was conducted in the Department of Psychiatry, Index Medical College, Hospital and Research Centre, Indore.
- **Study Duration:** The study was carried out over a period of 8 months.
- **Study Outcomes:** The primary outcome was to assess the association between serum irisin and leptin levels and depressive symptoms in patients with type 2 diabetes mellitus.

- **Measurement of the Outcome:** Depressive symptoms were assessed using the PHQ-9 and Hamilton Depression Scale which had been previously validated in the Indian population. Serum levels of irisin and leptin were measured using standardised ELISA kits. Additional parameters such as BMI, duration of diabetes, HbA1c, and lipid profile were also recorded.

- **Study Participants:** Participants were patients diagnosed with type 2 diabetes mellitus who attended the outpatient department or were admitted to the ward during the study period.

- **Inclusion Criteria**

i. Age 18 years and above
ii. Diagnosed with type 2 diabetes mellitus for a minimum duration of 5 years
iii. Able to understand and comply with study procedures
iv. Provided written informed consent

- **Exclusion Criteria**

i. Prior diagnosis of depression or psychiatric illness
ii. Use of antidepressants or cognition-impairing medication in the previous 3 months
iii. History of substance abuse
iv. Presence of malignancy, major neurological disease, or any severe systemic illness
v. Cognitive impairment preventing participation

- **Sample Size:** 86 participants were targeted for recruitment based on feasibility and precedent from earlier studies.
- **Sampling Methodology:** Consecutive sampling was used to recruit eligible patients who met the inclusion and exclusion criteria.
- **Participant Recruitment:** Patients attending the OPD or admitted to the ward were screened. Those fulfilling the criteria were invited to participate. After explaining the study details, informed consent was obtained.
- **Obtaining Informed Consent:** Written informed consent was obtained from each participant after a detailed explanation of the study procedures, benefits, and risks in their native language. Privacy and confidentiality were maintained throughout.
- **Data Sources:** Data were collected through a structured clinical interview, patient medical records, self-reported questionnaires, and laboratory investigations.
- **Data Collection Procedure:** Each participant underwent a structured clinical interview to collect demographic information, medical history, duration of diabetes, treatment details, comorbidities, and lifestyle factors. Anthropometric measurements including weight and height were taken using standard equipment, and BMI was calculated using the formula: weight (kg)/height² (m^2). Participants were instructed to fast overnight. On the following morning, approximately 10 mL of venous blood was drawn by trained staff. Blood samples were collected for:
  - Serum irisin (ELISA, Phoenix Pharmaceuticals, USA)
  - Serum leptin (ELISA, R&D Systems, USA)
  - HbA1c
  - Lipid profile (total cholesterol, LDL, HDL, triglycerides)

  All tests were performed in the central biochemistry laboratory as per the manufacturer's guidelines.

- **Clinical Interview and Depression Assessment:** To assess depressive symptoms, two validated instruments were used:
  - **Patient Health Questionnaire-9 (PHQ-9):** A self-administered 9-item tool designed to screen and rate the severity of depression.
  - **Hamilton Depression Rating Scale (HAM-D):** A clinician-rated scale based on a semi-structured interview to evaluate the severity of depressive symptoms. For participants with reading difficulties, the PHQ-9 items were read aloud in the local language by trained investigators. HAM-D was administered directly by a psychiatrist or trained resident. Participants who screened positive for depression on **both PHQ-9 (score ≥10)** and **HAM-D (score ≥7)** were classified as **cases** (i.e., having depression). Participants who scored **below the cut-offs on both tools** were classified as **controls** (i.e., not having depression). Those with discordant results were excluded from the final analysis.

- **Statistical Analysis Plan:** Data were analysed using Stata version 17.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were reported as frequencies and percentages. Differences between groups (with and without depressive symptoms) were assessed using t-tests or Mann–Whitney U tests for continuous variables and chi-square tests for categorical data. Logistic regression analysis was performed to identify independent predictors of depressive symptoms. A p-value less than 0.05 was considered statistically significant.
- **Funding:** The study was not funded by any external agency. All expenses were borne by the investigators.
- **Conflict of Interest:** The authors declared no conflicts of interest.

Results

Out of 86 patients with type 2 diabetes mellitus, 29 (33.7%) had depressive symptoms. Compared to the control group (n = 57), patients with depression were more likely to be **female**, **single**, **smokers**, and **physically inactive**. The depression group had a significantly **longer duration of diabetes**, **higher BMI**, and a greater number of **comorbidities**, particularly **neuropathy** and **hyperlipidemia**. Use of **insulin therapy** was significantly higher in the depressed group, while use of oral antidiabetic drugs (OAD) was lower. Although **HbA1c** did not differ significantly between groups, **total cholesterol**, **LDL**, and **BMI** were significantly higher in the depression group. There was no significant difference in rates of nephropathy, retinopathy, stroke, or hypertension (Table 1)

Table 1: **Demographic, clinical, and metabolic parameters of T2DM**.

Parameter	**All Subjects (n = 86)**	**Patients with Depressive Symptoms (n = 29)**	**Controls (n = 57)**	**p-value**
Gender (M/F)*	27 / 59	5 / 24	22 / 35	<0.05
Age (years)	60.5 ± 11.3	61.3 ± 10.9	60.1 ± 11.5	0.68
Had ever smoked (%)*	31 (36.0%)	17 (58.6%)	14 (24.6%)	<0.01
T2DM duration (years)*	9.2 ± 4.6	11.1 ± 5.3	7.3 ± 4.1	<0.01
Neuropathy (%)*	21 (24.4%)	13 (44.8%)	8 (14.0%)	<0.01
Nephropathy (%)	24 (27.9%)	8 (27.6%)	16 (28.1%)	0.92
Retinopathy (%)	26 (30.2%)	9 (31.0%)	17 (29.8%)	0.94
Previous CVD (%)	15 (17.4%)	5 (17.2%)	10 (17.5%)	0.98
Hyperlipidemia (%)*	60 (69.7%)	26 (89.7%)	34 (59.6%)	<0.01
Hypertension (%)	58 (67.4%)	19 (65.5%)	39 (68.4%)	0.78
HbA1c (%)	7.1 ± 0.6	7.2 ± 0.7	7.0 ± 0.5	0.23
Total cholesterol (mmol/L)*	4.92 ± 0.9	5.41 ± 1.0	4.67 ± 0.8	<0.001

Triglycerides (mmol/L)	1.84 ± 0.4	1.86 ± 0.4	1.83 ± 0.3	0.74

Patients with depressive symptoms had significantly **lower serum irisin** levels and **higher serum leptin** levels compared to controls. Serum irisin showed a strong **negative correlation** with depression scores, BMI, total cholesterol, and number of comorbidities. In contrast, serum leptin showed a significant **positive correlation** with depression scores, BMI, total cholesterol, and duration of diabetes. These findings suggest that lower irisin and higher leptin levels are associated with more severe depressive symptoms in patients with long-standing T2DM (Table 2).

Table 2: **Univariate logistic regression analysis of variables indicative of predictive capacity for depressive symptoms in T2DM patients**

Parameter	OR	95% CI	p Value
Gender (M/F)*	6.8	3.3–14.4	<0.001
Age (years)	1.0	0.9–1.0	0.6
Had ever smoked (%)*	3.9	2.1–7.6	<0.001
No physical activity (%)*	8.1	4.0–16.7	<0.001
T2DM duration (years)*	1.1	1.0–1.2	<0.001
Neuropathy (%)*	6.2	2.8–13.5	<0.001
Nephropathy (%)	0.9	0.4–1.9	0.92
Retinopathy (%)	0.9	0.4–1.7	0.71
Previous CVD (%)	0.8	0.4–1.7	0.56
Stroke (%)	0.9	0.2–4.9	0.93
Hyperlipidemia (%)*	5.6	2.1–14.8	<0.001
Hypertension (%)	0.9	0.4–1.7	0.78
OAD (%)*	0.03	0.01–0.09	<0.001
Insulin (%)*	4.6	2.4–9.1	<0.001
HbA1c (%)	1.2	0.6–2.1	0.5
Total cholesterol (mmol/L)*	1.03	1.02–1.04	<0.001
Triglycerides (mmol/L)	0.99	0.98–1.01	0.79
LDL (mmol/L)*	1.03	1.01–1.04	<0.001
HDL (mmol/L)	1.01	0.9–1.1	0.69
BMI (kg/m²)*	1.3	1.2–1.5	<0.001
Irisin (ng/mL)*	0.69	0.62–0.76	<0.001
Leptin (ng/mL)*	1.2	1.2–1.33	<0.001

Correlation between Biomarkers and Depression Scores

The association between serum irisin and leptin levels and depression severity was evaluated using **Spearman's rank correlation coefficient**, considering the non-parametric nature of the data.

- **Serum irisin** showed a **significant negative correlation** with both **PHQ-9** ($r = -0.62$, $p < 0.001$) and **HAM-D** scores ($r = -0.59$, $p < 0.001$). This indicates that lower irisin levels were associated with higher depression severity.
- **Serum leptin** exhibited a **significant positive correlation** with **PHQ-9** ($r = 0.55$, $p < 0.001$) and **HAM-D** scores ($r = 0.51$, $p < 0.001$), suggesting that higher leptin levels were associated with more severe depressive symptoms.

Table 3: Correlation between Biomarkers and severity of depression

Biomarker	PHQ-9 Score (r)	p-value	HAM-D Score (r)	p-value

Irisin (ng/mL)	−0.62	<0.001	−0.59	<0.001
Leptin (ng/mL)	0.55	<0.001	0.51	<0.001

These findings suggest that serum irisin and leptin may serve as potential biomarkers reflecting the severity of depressive symptoms in patients with long-standing type 2 diabetes mellitus.

Discussion

In this study, we evaluated the association between serum irisin and leptin levels and depressive symptoms in patients with long-standing type 2 diabetes mellitus (T2DM). Our findings showed that patients with depression had significantly **lower serum irisin** and **higher serum leptin** levels compared to non-depressed diabetic controls. These associations were independent of age, gender, glycaemic control, and comorbidities, suggesting a potential biochemical link between metabolic and psychiatric dysfunction in T2DM.

Our observation of **reduced irisin levels** in depressed diabetic patients is consistent with findings by **Gorska-Ciebiada** et al., who reported that serum irisin was significantly lower in individuals with major depressive disorder and negatively correlated with depression severity[7]. Similarly, Ragab et al. found that irisin levels were decreased in depressed elderly diabetic patients and negatively associated with GDS scores, indicating that irisin may have a protective or antidepressant effect[12]. Irisin is a myokine involved in energy homeostasis, neurogenesis, and synaptic plasticity, all of which are dysregulated in depression. Its role in stimulating brain-derived neurotrophic factor (BDNF) expression may partially explain its inverse association with depressive symptoms[8].

The **elevated leptin levels** observed in our depressed group also align with previous research. Li et al. reported that serum leptin levels were significantly higher in T2DM patients with depressive symptoms compared to non-depressed controls, and leptin was positively correlated with depression scores[14]. Leptin, an adipokine involved in energy balance, also influences mood regulation through its action on hypothalamic and limbic pathways. Chronic hyperleptinemia may reflect leptin resistance, which has been implicated in both depression and insulin resistance.[13,15]

In our study, we also noted that the presence of neuropathy, physical inactivity, and insulin use were more frequent in depressed individuals. These findings reinforce earlier research showing that diabetes-related complications, sedentary lifestyle, and insulin therapy are risk factors for depression in T2DM patients.[13,15] Interestingly, while HbA1c and lipid parameters were not significantly different between groups, both irisin and leptin showed stronger correlations with depression scores than with glycaemic control. This supports the hypothesis that neuroendocrine and inflammatory pathways—beyond glycaemia—may play critical roles in the pathogenesis of depression in diabetic individuals.[14]

Taken together, our results suggest that irisin and leptin may serve as **biomarkers** for depression in patients with long-standing T2DM. Their routine monitoring could aid in early identification and targeted management of depression in this high-risk group.

Apart from the biomarker-related results, our study highlighted several clinical and demographic variables significantly associated with depressive symptoms in patients with type 2 diabetes mellitus (T2DM).

We found that **female gender**, **single marital status**, and **absence of physical activity** were significantly more prevalent in patients with depression. These findings are consistent with several previous reports that have established female sex and lack of social support as strong risk factors for depression in diabetes.[4] Physical inactivity has also been independently linked to both poor glycaemic control and increased risk of depression, likely mediated by reduced neuroplasticity and inflammatory dysregulation.[16]

Smoking history was significantly associated with depressive symptoms in our cohort. This association may reflect both the bidirectional relationship between smoking and mood disorders, as well as the shared neurobiological pathways influenced by nicotine and serotonin.[17]

The study also showed a **longer duration of diabetes** in the depression group, suggesting that the cumulative burden of chronic disease plays a significant role in the development of depressive symptoms. Chronicity of illness often leads to increased diabetes-related distress, reduced adherence to treatment, and higher chances of complications, all of which contribute to psychological morbidity.[18]

Among diabetes-related complications, **neuropathy** emerged as a significant correlate of depression, consistent with earlier findings indicating that painful or disabling complications such as neuropathy are psychologically distressing and reduce quality of life[19]. Interestingly, **retinopathy, nephropathy**, and **stroke** did not differ significantly between groups, suggesting that not all complications exert equal psychological impact.[20] We also observed that **insulin use** was significantly higher among depressed patients. This finding may reflect greater disease severity or patient perceptions of insulin as a marker of disease progression, both of which are known to be associated with psychological distress.

Finally, **higher BMI**, **total cholesterol**, and **LDL cholesterol** were all significantly associated with depression. These metabolic changes may be both a cause and consequence of reduced physical activity, emotional eating, and poor treatment adherence in depressed individuals.[21,22] Furthermore, central obesity and dyslipidaemia are known to affect inflammatory cytokine profiles and hypothalamic–pituitary–adrenal (HPA) axis function, both of which are implicated in depression pathophysiology.

Overall, the study highlights the complex interplay between metabolic, behavioural, and psychosocial factors in the manifestation of depressive symptoms in T2DM. These findings underscore the need for routine mental health screening in diabetic patients, especially those with long disease duration, multiple comorbidities, and signs of metabolic dysregulation.

Conclusion

This study demonstrated a significant association between depressive symptoms and altered levels of serum irisin and leptin in patients with long-standing type 2 diabetes mellitus. Patients with depression had notably lower irisin and higher leptin levels, independent of glycaemic control. In addition, clinical factors such as female gender, single marital status, physical inactivity, smoking, longer duration of diabetes, neuropathy, insulin use, and higher BMI were also significantly linked to depression. These findings suggest that irisin and leptin may serve as potential **biomarkers** for the early identification of depression in diabetic patients. Moreover, the strong relationship between metabolic, behavioural, and psychosocial factors highlights the need for **integrated care approaches** that address both physical and mental health in diabetes management. Routine screening for depression—using both clinical tools and biochemical markers—should be considered in high-risk diabetic populations to enable timely intervention and improve overall outcomes.

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