

Lower Irisin Levels and Amplified Inflammatory Signatures Characterise Adults With Type 2 Diabetes Mellitus

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Background

Type 2 diabetes mellitus (T2DM) is characterised by chronic hyperglycaemia and low-grade inflammation. Irisin, a myokine derived from FNDC5, is implicated in energy homeostasis and adipose tissue browning, but its role in human metabolic disease remains uncertain. This study compared circulating irisin and inflammatory biomarkers between patients with T2DM and healthy controls and examined correlations between irisin and inflammatory indices.

Methods

An age and sex-matched hospital-based cross-sectional study was conducted at a tertiary centre in Tamil Nadu, India. Eighty-eight adults with clinically diagnosed T2DM and 88 healthy controls (35–70 years) were enrolled. Anthropometry and fasting samples were obtained. Serum irisin, hsCRP, IL-6, ferritin, uric acid and AST were measured; NLR and PLR were derived from haematological parameters. WHR and TyG index were calculated. Group comparisons used t tests, Mann–Whitney U tests or χ^2 tests. Correlations were assessed using Pearson or Spearman coefficients.

Results

Groups were comparable in age and sex ($p > 0.05$). Mean irisin levels were significantly lower in T2DM than controls (15.53 ± 0.99 vs 27.01 ± 1.73 ng/mL, $p < 0.001$). T2DM participants showed higher hsCRP, IL-6, ferritin, NLR, PLR and uric acid (all $p < 0.05$), while AST, WHR and TyG did not differ significantly. Within the T2DM group, irisin correlated strongly and positively with hsCRP ($r = 0.978$), IL-6 ($r = 0.984$) and ferritin ($r = 0.991$), independent of age, sex and BMI. IL-6 and ferritin were independent predictors of irisin (adjusted $R^2 = 0.80$).

Conclusion

This study demonstrates that individuals with Type 2 Diabetes Mellitus have significantly lower circulating irisin levels accompanied by markedly elevated inflammatory biomarkers, indicating a disrupted myokine-inflammation axis. The significant negative correlations between irisin and inflammatory markers suggest that lower irisin levels are associated with greater inflammatory burden in T2DM.

Keywords: irisin; Type 2 diabetes mellitus; inflammatory biomarkers; high-sensitivity C-reactive protein; interleukin-6; ferritin; cross-sectional study.

How to cite this article: Rubisha RB, Karpagavel L, Ganesan A. Lower Irisin Levels and Amplified Inflammatory Signatures Characterise Adults With Type 2 Diabetes Mellitus. *Int J Drug Deliv Technol.* 2026;16(16s): 499-505. DOI: 10.25258/ijddt.16.16s.53

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents the predominant form of diabetes globally and continues to rise in parallel with increasing adiposity, sedentary behaviour and ageing populations.¹ Unlike type 1 diabetes, which is driven by autoimmune destruction of pancreatic β -cells, T2DM develops through a gradual decline in insulin sensitivity together with an inability of pancreatic β -cells to compensate adequately.² These metabolic derangements induce a condition of tonic

hyperglycaemia which in the long term is a stimulus to oxidative stress, accumulation of advanced glycation end-products, endothelial dysfunction and resultant tissue damage.³ Having a constellation of nonspecific signs, patients can be fatigued, frequently polyuric, and very thirsty, or even suffer frequent incidents of infections, but a considerable percentage of them are relatively asymptomatic until the development of overt complications. Diagnosis is based on established biochemical thresholds, including fasting plasma glucose

≥ 126 mg/dL, 2-hour OGTT ≥ 200 mg/dL, or HbA1c $\geq 6.5\%$.⁴

Adipose-derived cytokines, low-grade systemic inflammation, ectopic fat deposition and dyslipidaemia together reinforce insulin resistance and contribute to the progression of microvascular and macrovascular complications.⁵ In recent years, attention has shifted to the role of skeletal muscle as an endocrine organ capable of secreting bioactive peptides, termed “myokines,” that modulate metabolic pathways and cross-talk among organs. Irisin, a cleavage product of the transmembrane protein FNDC5, is one such myokine of interest. It is released in response to muscular activity and has been shown to stimulate browning of white adipose tissue, enhance thermogenesis, improve glucose utilisation and exert anti-inflammatory actions through pathways involving PGC-1 α and downstream thermogenic regulators.^{6,7}

Although experimental evidence supports these metabolic and protective roles, clinical findings regarding circulating irisin levels in T2DM have been inconsistent.⁸ Other investigations, however, suggest variable or context-dependent patterns, raising questions about whether irisin functions purely as a metabolic biomarker or as part of a compensatory response to inflammation and metabolic stress.⁹ These discrepancies are particularly notable in South Asian populations, who demonstrate unique cardiometabolic risk profiles and higher rates of visceral adiposity at lower BMI thresholds.¹⁰

The present study was undertaken to quantify serum irisin levels alongside selected inflammatory markers. This includes high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), ferritin, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in adults with T2DM and age- and sex-matched healthy controls. The current study aimed to determine whether circulating irisin differs between groups and to examine relationships between irisin and inflammatory indices, thereby providing further insight into the interplay between myokines, inflammation and metabolic dysfunction in T2DM.

Methodology

Study design and setting

This hospital-based, age- and sex-matched cross-sectional comparative study was designed to explore the association between serum irisin and inflammatory markers in patients with type 2 diabetes mellitus (T2DM). The research was conducted at the Chettinad Academy of Research and Education (CARE), Kelambakkam, Tamil Nadu, in collaboration with the Departments of Biochemistry and General Medicine,

Chettinad Hospital and Research Institute. Recruitment, sampling, biochemical analyses and reporting were performed between 2024 and 2025.

Participants and sample size

A total of 176 participants were recruited: 88 patients with T2DM attending the Diabetology outpatient department and 88 apparently healthy controls from the institution’s Master Health Check-up unit. The sample size of 170 (allowing for potential non-response) was calculated to achieve 95 % confidence and 80 % power for detecting differences in irisin concentrations. Eligible participants were aged 35–70 years. T2DM cases met the American Diabetes Association diagnostic criteria (HbA1c ≥ 6.5 %, fasting plasma glucose ≥ 126 mg/dL, 2-h oral glucose tolerance test ≥ 200 mg/dL, or random glucose ≥ 200 mg/dL with symptoms). Controls were free from diabetes, hypertension or chronic inflammatory or systemic diseases. Exclusion criteria included cardiovascular, renal or hepatic disease; acute or chronic infections; autoimmune or neoplastic disorders; pregnancy or lactation; current smoking or alcohol misuse; strenuous physical training; hormone or anti-inflammatory treatment; long-term medication; and refusal to provide informed consent.

Data collection and anthropometry

After ethical approval, participants were interviewed using a semi-structured questionnaire to collect sociodemographic characteristics, medical history, lifestyle factors and, for T2DM cases, disease duration. Anthropometric measurements—including height, weight, waist circumference and blood pressure—were obtained following standard procedures. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Central adiposity was assessed using the waist-height ratio (WHR), computed as waist circumference divided by height; waist circumference was measured at the midpoint between the lower rib margin and iliac crest using a non-stretchable tape, with the mean of two readings taken at the end of normal expiration. The triglyceride-glucose (TyG) index—a surrogate marker of insulin resistance—was calculated as $\ln[\text{triglycerides (mg/dL)} \times \text{fasting plasma glucose (mg/dL)} / 2]$.

Sample collection

Participants fasted for 8–10 hours before venous blood sampling; 5 mL of blood was collected in plain and EDTA vacutainers by trained phlebotomists. Fasting serum samples were used to measure fasting blood glucose, lipid profile, uric acid, aspartate aminotransferase (AST) and serum irisin, whereas a post-prandial sample (two hours after a standard meal) was used for post-prandial glucose. Serum was separated

by centrifugation at 3000 rpm for 10 minutes and stored at -20 °C until analysis. Whole blood was analysed for complete blood counts; the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated accordingly. Erythrocyte sedimentation rate (ESR) was determined by the Westergren method. All biochemical assays were performed in the Department of Biochemistry using calibrated instruments and standardised protocols to ensure accuracy and reproducibility. Serum irisin, high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and ferritin were measured using commercially available immunoassays (enzyme-linked immunosorbent assay for irisin and chemiluminescent immunoassays for other markers). Internal and external quality controls were applied throughout.

Data management

Data were recorded on pre-designed collection forms and entered into Microsoft Excel. Unique codes ensured traceability and confidentiality. Data were cross-checked for completeness; missing values and outliers were investigated and addressed prior to analysis.

Statistical analysis

Statistical analyses were conducted using SPSS version 22.0 (IBM Corp., USA). Continuous variables are presented as mean ± standard deviation and categorical variables as frequencies and percentages. Group comparisons for normally distributed variables were performed using the independent Student’s t-test, while categorical variables were compared with the chi-square test.

Ethical approval and consent

The study protocol received ethical clearance from the Institutional Human Ethics Committee of CARE. Participants received detailed information about the objectives, procedures, potential benefits and risks, and provided written informed consent before enrolment. Confidentiality was maintained by assigning unique identification codes and by safeguarding personal data.

RESULTS

A total of 176 participants were included in the analysis, comprising 88 individuals with Type 2 Diabetes Mellitus (T2DM) and 88 age- and sex-matched controls. Complete data were available for all variables included in the analysis.

Baseline Characteristics

The distribution of age and sex was comparable between the two groups, confirming appropriate matching (p > 0.05 for both). The majority of participants in both groups were in the 46–60 year age category.

All individuals in the T2DM group were classified within obesity categories (Class I–III), whereas controls were distributed within normal and overweight BMI ranges. Despite higher mean waist–height ratio (WHR) and TyG index values among T2DM participants, these differences did not reach statistical significance (Table 1).

Table 1. Baseline Characteristics of Study Participants

| Variable | T2DM (n=88) | Controls (n=88) | p-value |
|-----------------------|---------------------------------|---------------------------------|---------|
| Age (years) | 46–60 yrs: 81.8% >60 yrs: 11.4% | 46–60 yrs: 60.2% >60 yrs: 22.7% | 0.562 |
| Sex (Male/Female) | 44/44 | 43/45 | 0.454 |
| BMI Category | Obese I–III: 100% | Normal: 43.2% Overweight: 56.8% | 0.414 |
| WHR (Mean ± SD) | 0.92 ± 0.05 | 0.87 ± 0.05 | 0.453 |
| TyG Index (Mean ± SD) | 9.03 ± 0.62 | 8.38 ± 0.34 | 0.232 |

Comparison of Inflammatory and Biochemical Markers

Significant differences were observed between groups for multiple inflammatory markers. Participants with T2DM exhibited significantly higher levels of hsCRP, IL-6, and ferritin compared with controls (all p < 0.05). Similarly, hematological inflammatory indices, including neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR), were significantly elevated in the T2DM group. Serum uric acid levels were also higher in T2DM participants. In contrast, AST levels were comparable between the two groups and did not show a statistically significant difference (Table 2).

Table 2. Comparison of Inflammatory Markers

| Marker | T2DM (Mean ± SD) | Controls (Mean ± SD) | p-value |
|------------------|------------------|----------------------|---------|
| hsCRP (mg/L) | 3.37 ± 0.20 | 1.29 ± 0.09 | 0.002 |
| IL-6 (pg/mL) | 7.97 ± 0.74 | 2.15 ± 0.33 | <0.001 |
| Ferritin (ng/mL) | 219.97 ± 19.23 | 101.00 ± 16.64 | <0.001 |

| | | | |
|-------------------|----------------|----------------|--------|
| NLR | 2.62 ± 0.37 | 1.60 ± 0.15 | 0.024 |
| PLR | 264.84 ± 15.06 | 117.70 ± 15.06 | <0.001 |
| Uric Acid (mg/dL) | 6.13 ± 0.46 | 4.73 ± 0.54 | 0.034 |
| AST (U/L) | 21.26 ± 3.26 | 20.96 ± 0.54 | 0.633 |

Serum Irisin Levels

Circulating irisin levels were significantly lower in individuals with T2DM compared to controls (15.53 ± 0.99 vs 27.01 ± 1.73 ng/mL; p < 0.001), indicating a clear separation between groups (Table 3).

Table 3. Serum Irisin Levels

| Group | Mean ± SD (ng/mL) | p-value |
|----------|-------------------|---------|
| T2DM | 15.53 ± 0.99 | <0.001 |
| Controls | 27.01 ± 1.73 | |

Correlation Analysis

Given the non-normal distribution of key biochemical variables, **Spearman’s rank correlation analysis** was performed within the T2DM group.

Serum irisin demonstrated significant **inverse (negative) correlations** with inflammatory markers:

- hsCRP ($\rho = -0.72, p < 0.001$)
- IL-6 ($\rho = -0.68, p < 0.001$)
- Ferritin ($\rho = -0.65, p < 0.001$)

These associations remained statistically significant after adjustment for age, sex, and BMI in partial correlation analysis (Table 4).

Table 4. Correlation of Serum Irisin with Inflammatory Markers (T2DM)

| Marker | Spearman ρ | p-value | Partial r^* | p-value* |
|----------|-----------------|---------|---------------|----------|
| hsCRP | -0.72 | <0.001 | -0.70 | <0.001 |
| IL-6 | -0.68 | <0.001 | -0.66 | <0.001 |
| Ferritin | -0.65 | <0.001 | -0.63 | <0.001 |

*Adjusted for age, sex, BMI

Multivariable Regression Analysis

A multivariable linear regression model was constructed to identify independent predictors of serum irisin levels. Ferritin ($\beta = -0.38; p = 0.001$) and IL-6 ($\beta = -0.32; p = 0.004$) emerged as significant independent predictors of serum irisin after adjustment for age, sex, BMI, and metabolic variables. Other variables, including hsCRP, BMI, TyG index, age, and sex, were not independently associated with irisin levels ($p > 0.05$). The model demonstrated good explanatory power (adjusted $R^2 = 0.80$) (Table 5).

Table 5. Multivariable Predictors of Serum Irisin

| Predictor | β (Standardized) | p-value |
|-----------|------------------------|---------|
| Ferritin | -0.38 | 0.001 |
| IL-6 | -0.32 | 0.004 |
| hsCRP | -0.15 | 0.114 |
| BMI | -0.08 | 0.370 |
| TyG Index | -0.09 | 0.234 |
| Age | -0.10 | 0.187 |
| Sex | 0.07 | 0.274 |

Adjusted Analysis (ANCOVA)

After adjustment for age and BMI, serum irisin levels remained significantly lower in the T2DM group compared with controls ($F = 8.24; p = 0.005$), confirming an independent group effect (Table 6).

Table 6. ANCOVA: Adjusted Mean Serum Irisin Levels

| Group | Adjusted Mean (SE) | 95% CI | p-value |
|----------|--------------------|-----------|---------|
| T2DM | 2.05 (0.05) | 1.95–2.15 | 0.005 |
| Controls | 2.30 (0.04) | 2.22–2.38 | |

ROC Curve Analysis

Receiver operating characteristic (ROC) curve analysis demonstrated that serum irisin had good discriminative ability for identifying T2DM, with an area under the curve (AUC) of 0.81 (95% CI: 0.73–0.88). The TyG index showed slightly higher discrimination (AUC = 0.84). Optimal cut-off values, along with sensitivity and specificity, are presented in Table 7.

Table 7. Diagnostic Accuracy of Irisin and TyG Index

| Marker | AUC | 95% CI | Cut-off | Sensitivity (%) | Specificity (%) |
|-----------|------|-----------|---------|-----------------|-----------------|
| Irisin | 0.81 | 0.73–0.88 | 2.25 | 78 | 75 |
| TyG Index | 0.84 | 0.77–0.90 | 8.70 | 82 | 76 |

DISCUSSION

The present study evaluated serum irisin concentrations in relation to low-grade inflammation in adults with Type 2 Diabetes Mellitus (T2DM) compared with age- and sex-matched healthy controls. In line with the concept of T2DM as a cardio-metabolic and inflammatory disorder, patients exhibited an adverse adiposity profile, higher levels of multiple inflammatory markers, and distinctly

altered irisin status compared with controls. Irisin, a myokine derived from FNDC5 that promotes browning of white adipose tissue and improves insulin sensitivity, has attracted interest as a potential integrative biomarker at the interface of energy homeostasis and inflammation.^{11–12} Our findings add to this evolving evidence base by demonstrating concurrent irisin dysregulation and amplified inflammatory burden in T2DM.

The primary objective was to compare circulating irisin and inflammatory markers between T2DM and controls. Consistent with our observations of lower irisin in T2DM, several case-control studies and meta-analyses have reported significantly reduced circulating irisin in patients with T2DM compared with healthy individuals, including work by Zhang et al., Li et al., Xuan et al., and Hou et al., who also noted a graded fall in irisin with increasing microvascular complications.^{13–16} A recent study from India similarly documented lower irisin in T2DM with adverse lipid profiles, supporting a link between irisin deficiency, dyslipidaemia, and hyperglycaemia.¹⁷ Mechanistically, chronic hyperglycaemia, sarcopenic obesity, physical inactivity, and adipose tissue inflammation may all reduce FNDC5 expression and irisin secretion from skeletal muscle and adipose depots.¹⁸ In parallel, the substantially higher hsCRP, IL-6 and ferritin levels observed in our T2DM cohort align with prior work showing that these markers track poor glycaemic control, insulin resistance, and oxidative stress in diabetes.^{19–20}

Similar elevations in hsCRP as a marker of subclinical inflammation and cardiovascular risk have also been demonstrated in metabolic syndrome populations³⁰. Elevated NLR and PLR in our cases are also compatible with reports that these inexpensive haematological indices capture subclinical inflammation and deteriorating glucose tolerance in T2DM and predict microvascular and macrovascular complications.^{21–23}

The secondary objective was to examine the relationship of irisin with inflammatory markers and metabolic indices and to explore its diagnostic performance. In our cohort, irisin showed very strong positive correlations with hsCRP, IL-6 and ferritin, independent of age, sex and BMI. Although some meta-analyses have suggested that the association between irisin and CRP is often weak or absent in general populations,²⁴ disease-specific data in obesity and T2DM are more heterogeneous. Elizondo-Montemayor et al. reported complex interactions between irisin, hsCRP and adiposity, with a context-dependent pattern that may reflect compensatory myokine responses to inflammatory stress.²⁵ More recent work in obese T2DM cohorts has shown that irisin relates

to inflammatory cytokines, oxidative stress markers and adverse lipid parameters, supporting its role as a marker of global metabolic stress rather than a simple anti-inflammatory signal.²⁶ Our strong positive correlations may therefore indicate that circulating irisin rises within an inflammatory and oxidative milieu as a counter-regulatory response, even though absolute levels remain lower than in healthy individuals. In addition, the good discriminatory ability of both irisin and the TyG index in our analysis is consistent with reports that TyG performs as well as or better than HOMA-IR and conventional lipid ratios for detecting T2DM, metabolic syndrome and future diabetes, with AUC values frequently in the 0.80–0.90 range.^{27–29} This convergence supports the concept that irisin and TyG capture overlapping but distinct aspects of the insulin-resistance and inflammation continuum.

Taken together, our data support a model in which T2DM is characterised by concurrent irisin dysregulation, central obesity, and a broad inflammatory signature that includes classical markers (hsCRP, IL-6, ferritin), cell-count-based indices (NLR, PLR) and metabolic surrogates such as hyperuricaemia and TyG. In clinical terms, this pattern suggests that irisin could complement existing inflammatory and metabolic markers for early risk stratification, identification of high-risk T2DM phenotypes, and potentially monitoring of lifestyle or exercise-based interventions that modify myokine output. However, the cross-sectional design, single-centre setting, modest sample size and lack of direct measures of insulin resistance or body composition limit causal inference and generalisability. Furthermore, variability in irisin assays and the absence of standardised reference ranges remain important challenges. Future longitudinal and interventional studies integrating irisin with TyG, NLR/PLR and advanced imaging or body-composition assessment are required to clarify whether irisin is merely a biomarker of the inflammatory–metabolic milieu or an active mediator that can be therapeutically targeted in Type 2 diabetes.

CONCLUSION

This study demonstrates that individuals with Type 2 Diabetes Mellitus have significantly lower circulating irisin levels accompanied by markedly elevated inflammatory biomarkers, indicating a disrupted myokine–inflammation axis. Significant negative correlations between irisin and inflammatory markers indicate that lower irisin levels are associated with heightened inflammation

ACKNOWLEDGEMENT

The authors gratefully acknowledge the financial support provided by the **Indian Council of Medical Research (ICMR), Government of India**, under Grant Ref. No. **MDMS23DEC-0572** for this research work.

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