International Journal of Biomedical Research Science (IJBRS)
An Open Access International Journal
Online ISSN: 3107-8745
Vol 02 No (1) Jan-Feb-Mar-Apr 2026

Iron Homeostasis and Insulin Resistance in Type 2 Diabetes: A Cross-Sectional Study

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ARTICLE INFO

Received Date: 15/01/2026
Accepted Date: 08/02/2026
Publication Date: 30th April 2026
Page Number:- 27-31
Available at: www.ijbrs.com

ABSTRACT:

Type 2 diabetes mellitus (T2DM) is closely associated with iron biology and oxidative stress. Indian data are, however, sparse regarding the association of abnormal iron indices, particularly hyperferritinemia, with insulin resistance and cardiometabolic risk. Iron status, glycaemia, dyslipidaemia, and oxidative stress in adults with T2DM receiving routine care were investigated in this thesis. (1) compared markers of iron homeostasis (ferritin, transferrin and total iron binding capacity [TIBC]) in adults with T2DM versus age-matched healthy controls; (2) examined the relationship of ferritin with insulin resistance (HOMA IR score) among subjects with well-controlled glycaemia and finally (3) profiled glycaemic indicators, apolipoproteins, inflammatory markers and oxidative stress biomarkers by disease status. A comparative cross-sectional study recruited 100 adults with T2DM and 100 age and sex matched controls (35–65 years). Anthropometry, blood pressure, fasting/post prandial glucose, HbA1c, lipid profile, ApoB/ApoA1, insulin (with HOMA IR), complete blood count, CRP, ESR, vitamins C and E, oxidative stress (MDA, SOD, GST), and iron indices (serum iron, ferritin, transferrin, TIBC) were obtained using standard biochemical and immunoturbidimetric methods; statistics used SPSS 20 with t tests and Pearson correlations (α=0.05).

Compared with controls, the T2DM group had higher BMI (24.83 ± 1.99 vs 23.54 ± 2.54 kg/m²; $p<0.01$) and blood pressure (SBP 134.05 ± 14.25 vs 123.69 ± 8.4 mmHg; DBP 83.12 ± 4.16 vs 80.1 ± 1 mmHg; both $p<0.01$). Fasting glucose (167.3 ± 51.56 vs 85.05 ± 8.54 mg/dL) and PPBS (216.06 ± 69.13 vs 114.15 ± 12.31 mg/dL) were higher (both $p<0.01$). Insulin (15.0 ± 10.21 vs 8.72 ± 11.29 µIU/mL) and HOMA IR (6.11 ± 4.70 vs 1.84 ± 2.40) were elevated ($p<0.01$). Ferritin was markedly higher (155.41 ± 31.91 vs 39.12 ± 21.45 ng/mL; $p<0.01$), while transferrin (244.31 ± 40.35 vs 280.94 ± 60.71 mg/dL; $p<0.01$) and TIBC (251.38 ± 67.72 vs 313.97 ± 64.79 µg/dL; $p<0.01$) were lower. Oxidative stress was higher (MDA 25.64 ± 12.81 vs 5.44 ± 6.04 nmol/mL; $p<0.01$) with lower SOD and GST and reduced vitamins C and E (all $p<0.01$). Ferritin correlated with HOMA IR ($r=0.424$; 95% CI 0.304–0.532; $p<0.001$) among those with satisfactory glycaemic control. Adults with T2DM showed a distinct iron inflammation–oxidative stress phenotype: higher ferritin (with lower transferrin/TIBC), stronger insulin resistance, and heightened oxidative stress. Ferritin's positive association with HOMA IR supports a role for iron dysregulation in insulin resistance in this Indian cohort.

KEY WORDS: Type 2 Diabetes Mellitus; Insulin Resistance; Serum Ferritin; Transferrin; TIBC; Oxidative Stress; Malondialdehyde; Apolipoprotein B.

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is increasing around the world, including India, with significant microvascular and macrovascular complications [1]. Indian patients generally exhibit a clustering of dyslipidaemia, hypertension, and inflammation, which enhances vascular risk [2]. In addition to glucose, iron has been identified as an essential mediator of metabolic risk [3]. Elevated ferritin has been linked to insulin resistance, β-cell stress, and unfavourable cardiometabolic phenotypes: in particular, the pathogenetic role of excessive labile iron-mediated production of reactive oxygen species (ROS) and protein glycation mechanisms that lead to impaired activity of the insulin receptor [4]. Data from cohort and mechanistic studies indicate that ferritin and transferrin kinetics (including reduction of Fe^{3+} binding to transferrin by glycation3) are impacted in diabetes, which can further create a vicious circle of oxidative stress and inflammation [5].

Oxidative stress is integral to diabetic vascular pathology: lipid peroxidation by products such as malondialdehyde (MDA) are elevated, while enzymatic antioxidants (e.g., SOD, GST) and antioxidant vitamins (C, E) may be depleted [6]. Dyslipidaemia (notably ApoB-rich lipoproteins) further compounds risk. Despite this, Indian data simultaneously profiling iron indices, insulin resistance, oxidative stress, and emerging lipid markers in a single study remain scarce [7].

Knowledge gap and rationale: While prior work has linked iron status to glucose dysregulation and cardiometabolic risk, there is limited integrative evidence from Indian outpatient populations receiving routine care—especially examining correlations between ferritin and insulin resistance under satisfactory glycaemic control. This study addresses that gap.

Objectives: We sought to (i) compare iron homeostasis markers between T2DM cases and matched controls; (ii) quantify the relationship between ferritin and HOMA IR; and (iii) characterise oxidative stress, antioxidant status, inflammatory markers, and apolipoproteins in the same cohort.

MATERIAL AND METHODS

Study design and setting: This was a comparative cross-sectional study conducted at a diabetic clinic, Kozhikode, Kerala, India, from December 2020 to May 2022.

Participants. Adults aged 35–65 years: 100 with previously diagnosed T2DM on treatment and 100 apparently healthy controls, matched by age and sex. Inclusion required willingness to participate; individuals with life-threatening comorbidities were excluded.

Data collection and assays: Anthropometry and blood pressure were recorded; fasting/post-prandial blood glucose (oxidase–peroxidase method) and lipid profile were measured. ApoB/ApoA1 were quantified by immunoturbidimetry. Oxidative stress was assessed via MDA (thiobarbituric acid reactive substances method) and antioxidant enzymes (SOD, GST); vitamins C and E were measured with standard spectrophotometric protocols. Insulin and HOMA IR were obtained; complete blood count, CRP, ESR, iron, ferritin, transferrin, and TIBC were analysed using standard laboratory methods.

Outcomes: Primary: between-group differences in ferritin, transferrin, and TIBC; association between ferritin and HOMA IR under satisfactory glycaemic control. Secondary: between-group differences in glycaemic, lipid, inflammatory, haematological, and oxidative stress indices.

Table 1. Baseline characteristics of participants (Control vs Test)

Parameter	Control (n=100)	Test (n=100)	t test	p value
Age (years)	47.5 ± 10.56	51.5 ± 10.32	−2.71	<0.01**
Height (cm)	161.94 ± 6.46	162.06 ± 7.58	−0.12	0.904
Weight (kg)	61.96 ± 7.82	64.55 ± 8.07	−2.30	<0.05*
BMI (kg/m²)	23.54 ± 2.54	24.83 ± 1.99	−4.01	<0.01**

Statistical analysis: Data are mean ± SD. Group comparisons used independent samples t tests; Pearson correlations examined relationships among ferritin, insulin, and HOMA IR. Significance was set at $p \leq 0.05$ (SPSS v20).

RESULTS

Participant characteristics: The T2DM group had higher BMI (24.83 ± 1.99 vs 23.54 ± 2.54 kg/m²; p<0.01) and blood pressure (SBP 134.05 ± 14.25 vs 123.69 ± 8.4 mmHg; DBP 83.12 ± 4.16 vs 80.1 ± 1 mmHg; both p<0.01).

Glycaemia and insulin resistance: FBS and PPBS were higher in T2DM (FBS 167.3 ± 51.56 vs 85.05 ± 8.54 mg/dL; PPBS 216.06 ± 69.13 vs 114.15 ± 12.31 mg/dL; both p<0.01). Insulin (15.0 ± 10.21 vs 8.72 ± 11.29 µIU/mL; p<0.01) and HOMA IR (6.11 ± 4.70 vs 1.84 ± 2.40; p<0.01) were elevated.

Lipid and apolipoprotein profile: Traditional lipids were higher in T2DM; ApoB was significantly higher (1.55 ± 0.19 vs 1.46 ± 0.17 g/L; p<0.01), while ApoA1 was modestly higher but not statistically significant (1.29 ± 0.33 vs 1.23 ± 0.13 g/L; p = 0.077).

Oxidative stress and vitamins: MDA was markedly higher (25.64 ± 12.81 vs 5.44 ± 6.04 nmol/mL; p<0.01). Antioxidant enzymes SOD (55.15 ± 37.90 vs 498.73 ± 671.12 U/L; p<0.01) and GST (21.31 ± 18.13 vs 74.89 ± 32.15 ng/mL; p<0.01) were lower. Vitamins C and E were significantly reduced (both p<0.01).

Table 2. Glycaemic parameters in Control vs Test

Parameter	Control (n=100)	Test (n=100)	t test	p value
FBS (mg/dL)	85.05 ± 8.54	167.30 ± 51.56	−15.74	<0.01**
PPBS (mg/dL)	114.15 ± 12.31	216.06 ± 69.13	−14.51	<0.01**
HbA1c (%)	4.87 ± 0.38	5.82 ± 1.16	−7.75	<0.01**

Table 3. Lipid profile in Control vs Test

Parameter	Control (n=100)	Test (n=100)	t test	p value
Total Cholesterol (mg/dL)	178.39 ± 13.57	231.60 ± 27.88	−17.16	<0.01**
HDL C (mg/dL)	47.22 ± 4.48	36.50 ± 3.03	19.80	<0.01**
LDL C (mg/dL)	111.92 ± 10.20	157.96 ± 26.70	−16.11	<0.01**
VLDL C (mg/dL)	20.75 ± 5.06	33.96 ± 11.15	−10.79	<0.01**
Triglycerides (mg/dL)	122.93 ± 18.84	177.46 ± 30.85	−15.08	<0.01**

Inflammation and haematology: CRP and ESR were higher in T2DM; total WBCs, neutrophils, lymphocytes, platelets, RBCs, haematocrit, and MCV were elevated, while MCH/MCHC/RDW indices showed no significant rise. Hb did not differ significantly.

Table 4. Oxidative stress and antioxidant markers

Parameter	Control (n=100)	Test (n=100)	t test	p value
MDA (nmol/mL)	5.44 ± 6.04	25.64 ± 12.81	−14.26	<0.01**
SOD (U/L)	498.73 ± 671.12	55.15 ± 37.90	6.60	<0.01**
GST (ng/mL)	74.89 ± 32.15	21.31 ± 18.13	14.52	<0.01**
Vitamin C (ng/mL)	93.08 ± 40.11	11.07 ± 7.71	20.08	<0.01**
Vitamin E (nmol/mL)	64.94 ± 21.45	7.80 ± 5.42	25.83	<0.01**

Iron homeostasis: Ferritin was substantially higher in T2DM (155.41 ± 31.91 vs 39.12 ± 21.45 ng/mL; p<0.01), whereas transferrin (244.31 ± 40.35 vs 280.94 ± 60.71 mg/dL; p<0.01) and TIBC (251.38 ± 67.72 vs 313.97 ± 64.79 µg/dL; p<0.01) were lower. Among participants with satisfactory glycaemic control, ferritin correlated with HOMA IR (r=0.424; p<0.001) and with insulin (r=0.214; p=0.002). Insulin correlated strongly with HOMA IR (r=0.848; p<0.001).

DISCUSSION

In this clinic-based Indian cohort, T2DM was characterised by higher adiposity and blood pressure; marked hyperglycaemia with elevated insulin/HOMA IR; an atherogenic lipid pattern with higher ApoB; pronounced oxidative stress (high MDA; low SOD/GST and vitamins C/E); systemic inflammation (CRP/ESR); and a distinct iron signature—high ferritin with lower transferrin/TIBC. Significantly, ferritin correlated positively with HOMA IR under satisfactory glycaemic control, strengthening the link between iron stores and insulin resistance. Our results are consistent with previous evidence that has associated ferritin with insulin resistance and T2DM risk [8]. Harrison et al. emphasized the involvement of iron in glucose toxicity and insulin action [9]. A meta-analysis by Yang et al. supported the relationship between abnormal iron homeostasis and T2DM [10].

Conway et al. In population studies, body iron was independently associated with serum insulin and glucose [11]. While mechanistically hepcidin is known to modulate iron flux, transferrin glycation may reduce the binding capacity of iron and increase labile iron, leading to ROS and inflammation – consistent with our high ferritin and oxidative stress [12].

The documented lower transferrin/TIBC in T2DM likely mirrors inflammation-induced negative acute phase-reactants and glycation-mediated function impairment of transferrin, as evidenced by in vitro and clinical studies. In concert, they may attenuate iron binding and exaggerate oxidative damage in line with our increased MDA and depleted antioxidant levels. Our pattern of oxidative stress—increased MDA, decreased SOD/GST, and lower vitamins C/E—is consistent with traditional diabetes reports and newer endothelial/metabolic dysregulation studies that emphasize ROS damage.

On lipids, ApoB no question complements the idea that higher ApoB is better than LDL C as a risk marker, significant in DM, where dense LDL rules the roost. Discrepancies with some literature (for example, the lack of a substantial increase in ApoA1 in our study) may result from the status of treatment, diet, or background inflammation in our cohort.

Strengths are age/sex matching, a large biomarker panel (glycaemic, lipid, inflammatory-oxidative-iron indices), and formal correlation of ferritin against insulin resistance over an interval clinically pertinent. The thesis addressed these limitations: cross-sectional nature (i.e., no causality), single-centre recruitment, incomplete formal risk assessment for diabetic complications, and potential residual confounding (dietary iron; hepcidin status; medication effects). Limitations Analytic choices (e.g., use of HOMA IR rather than clamp studies; lack of measurement of hepcidin levels) limit mechanistic inference.

CONCLUSION

This study demonstrates that, in Indian adults with T2DM, iron dysregulation (high ferritin with lower transferrin/TIBC) coexists with insulin resistance and heightened oxidative stress. Ferritin relates positively to HOMA IR under satisfactory glycaemic control. These data support integrating iron indices into cardiometabolic risk appraisal and motivate prospective/interventional work (e.g., defining optimal ferritin targets, clarifying hepcidin dynamics) in Indian settings.

ACKNOWLEDGMENTS

The authors thank the participants and the clinical and laboratory staff of the Sevana Clinic, Kozhikode, for their support with recruitment, sample processing, and data capture.

Funding: No external funding is reported in the provided thesis text. If institutional or grant support was received, please insert the details here.

Authors' contributions: The thesis author undertook conceptualization, methodology, investigation, and data curation; supervision by the faculty advisors; formal analysis and drafting of the present article based on the thesis dataset were performed as described herein. All authors approved the final manuscript.

Conflict of interest: The authors declare no competing interests.

Data availability: The identified data underlying this study's findings (biomarker matrices and statistical code) are available from the corresponding author upon reasonable request, subject to ethical approvals and institutional policies.

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