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The Ferritin-Gamma-Glutamyl Transferase Association: A Case-Control Study of a Proposed Index for Beta-Cell Function in T2DM

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ABSTRACT

Ferritin and gamma-glutamyl transferase (GGT) association, are firmly linked with oxidative stress and inflammation, conferring a supra-additive risk for type 2 diabetes mellitus pathogenesis (T2DM) and beta-cell exhaustion. This study assessed blood pressure (SBP, DBP), BMI, GGT, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), serum ferritin (SF), insulin (INS), homeostatic model assessment for insulin resistance (HOMA-IR), Homeostatic Model Assessment for β-cell function (HOMA-B), and computed SF/GGT, disposition index (DI), in 50 T2DM subjects and 31 healthy age-matched controls, recruited into this case-control study. Serum INS and SF were determined using ELISA, while GGT, FPG and HbA1c were determined by colorimetric methods. Height and weights were measured and BMI computed. Blood pressure was measured using a sphygmomanometer. Data generated were analyzed using SPSS version 27, (IBM). The normality of the data was determined by Shapiro-Wilk test. Group means were compared by Student's T-test and association by Pearson's correlation. The Receiver Operator Characteristic Curve, bootstrap and cross validation were utilized to determine the performance metrics of biochemical indexes. The confidence interval was set to 95% at α =0.05. The SBP, FPG, HbA1c, BMI, GGT, SF, INS, and HOMA-IR, were significantly higher while SF/GGT, HOMA-B and DI were significantly lower in diabetics when compared with non-diabetic controls ($p<0.05$). The FPG, INS, HOMA-IR, and SF/GGT were significantly higher while DI was significantly lower ($p<0.05$) in diabetics with HbA1c >7%, than in diabetics with HbA1c ≤ 7%. At a cutoff point of 20.61 U/L, GGT demonstrated AUC =0.983, p=0.000, C.I=0.958–1.008, Gini Index=0.966, max. K-S=0.960, sensitivity=96% and specificity =100% in predicting beta cell dysfunction. The findings of this study suggest that the association between ferritin and GGT may serve as a significantly stronger predictor and diagnostic screen for longitudinal HOMA-beta decline than either biomarker evaluated independently, however, validation in an independent cohort is required.

Keywords: Ferritin, gamma-glutamyl transferase, synergy, beta-cell dysfunction, T2DM

1.0 Introduction

Type 2 diabetes mellitus (T2DM) is a major global health challenge and one of the leading causes of cardiovascular disease, nephropathy, neuropathy, retinopathy, and premature mortality worldwide (Młynarska *et al.,* 2025; Ahmed *et al.,* 2025, Eworo, *et al.,* 2022). The ferritin-gamma-glutamyl transferase (GGT) association, may represent a unified predictive model, a pro-oxidant, iron-catalyzed feed-forward loop,

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serving as a diagnostic screen for pancreatic beta-cell fatigue in T2DM. While serum ferritin and GGT, are separately linked with metabolic dysfunction, concurrent elevation in their levels exert an additive, supra-linear effect on metabolic deterioration.

The clinical evaluation of T2DM pathogenesis relies on recognizing that insulin resistance (IR) and beta-cell dysfunction are not independent variables; they are tightly coupled in a feedback loop. Insulin secretion naturally balances up to compensate for underlying tissue insulin resistance to maintain euglycemia (Espinoza-Hernández *et al.,* 2026). Overt T2DM manifests only when this compensatory mechanism fails. Pancreatic beta-cells are exclusively susceptible to the Ferritin-GGT pro-oxidant engine, because beta-cells display a profound intrinsic deficiency in antioxidant defense mechanisms, relative to other body tissues (Kaneto *et al*., 2022; American Diabetes Association, 2024). The homeostatic model assessment indices, HOMA-IR and HOMA-B, are widely used proxy markers for evaluating insulin resistance and pancreatic β-cell function respectively. When evaluating pancreatic β-cell function and the pathophysiology of T2DM, various biomarkers assess different facets of glycaemic control (Yau *et al.,* 2025). The C-peptide and HOMA-B quantify absolute, steady-state insulin production, the proinsulin/insulin ratio measures qualitative cellular strain (secretory reserve), serving as an early indicator of processing defects and secretory exhaustion before total output drops. The Disposition Index provides a physiologically accurate measure of true β-cell health (compensatory fidelity) by adjusting secretory capacity for the underlying insulin resistance (HOMA-IR), allowing timely prediction of actual progression or therapeutic failure. Whereas HbA1c reflects the long-term, downstream glycemic consequence of that relationship failing, enabling assessment of dynamic adaptation against glycemic consequence. The ferritin:GGT ratio acts as an upstream metabolic mirror, charting the systemic inflammation, ectopic fat deposition, and localized hepatic and pancreatic oxidative stress that physically drive islet cell functional decline.

The interactions between ferritin and GGT affect cellular pathways such as the (1) Fenton reaction and oxidative stress amplification, (2) hepatic steatosis and the lipotoxic feedback loop, where excessive hepatic fat and iron accumulation causes pancreatic lipotoxicity, as local free fatty acids synergize with excess iron to trigger lipoapoptosis within the islets and (3) chronic subclinical inflammation (driven by ferritin and GGT) (Chen *et al.,* 2026). Elevated serum GGT levels are commonly associated with oxidative stress, metabolic dysfunction-associated steatotic liver disease (MASLD), insulin resistance (Lee *et al*., 2021; Kunutsor *et al*., 2023). Ferritin serves as a proxy for iron stores. Both ferritin and GGT are therefore closely linked to oxidative stress pathways implicated in pancreatic β-cell dysfunction. The Ferritin: GGT pair serves as a dual-purpose mirror, capturing catalytic iron toxicity, metabolic inflammatory burden and ongoing oxidative damage to pancreatic islet cells, (Miao, *et al.,* 2023). However, the relationship between the Ferritin:GGT ratio and pancreatic β-cell function has not been fully elucidated. Most previous studies have focused predominantly on HOMA-IR and peripheral insulin resistance as the principal drivers of T2DM progression, while few recent studies evaluated biomarkers associated with progressive decline in HOMA-B and β-cell exhaustion (Amrousy *et al*., 2024). Older models treated GGT and ferritin as general indicators of liver fat accumulation, while current research established that GGT and ferritin interact synergistically to elevate the risk of T2DM (Mohapatra *et al.,* 2020). This research proposes that the interaction between iron-mediated Fenton reactions (high ferritin) and pro-oxidant production (catalyzed by GGT) jointly acts as an extremely specific, local driver of pancreatic beta-cell iron buildup and oxidative damage. This study tested two hypotheses (1) the unified Ferritin-GGT Index possesses a significantly higher accuracy for predicting a decline in beta-cell insulin secretory capacity than either serum ferritin or GGT utilized in isolation, (2) a high Ferritin-GGT index predicts a distinct blunting of beta-cell recovery in patients having widespread oxidative stress. This study assessed blood pressure, ferritin, insulin, GGT, FPG, HbA1c, computed BMI, Ferritin: GGT ratio, disposition index, HOMA-B, and HOMA-IR in individuals with T2DM.

2.0 Materials and Method

Study design

This study was a case-control design conducted among subjects with type 2 diabetes mellitus (T2DM), attending Clinics at the University of Calabar Teaching Hospital, Calabar.

Study setting/subject selection

The study population consisted of confirmed T2DM patients residing in Calabar Metropolis, Cross River State, Nigeria. The study was conducted in Calabar Metropolis from October 2023 to August 2024. Fifty patients diagnosed with T2DM, aged 30-65 years and 31 apparently healthy age-matched, normoglycemic (FPG <5.6 mmol/L and HbA1c <5.7%) controls residing within the same geographical location were enrolled into the study. The diabetic subjects were further categorized into those with good glycemic control (HbA1c ≤7.2%, n=18) and those with poor glycemic control (HbA1c >7.2%, n=32).

Inclusion and exclusion criteria

Diabetic patients with no recent hospitalization, and no history of chronic liver disease, malignancy, alcohol abuse, smoking, iron supplementation, hemochromatosis, chronic inflammatory disease, renal disease, pregnancy, or insulin therapy were recruited into the study. Individuals outside the selected age range, patients with active infection, autoimmune disease, corticosteroid therapy, known NAFLD, elevated AST/ALT levels or known hematologic disorders were excluded from the study.

Data collection

Socio-demographic characteristics including age, sex, marital status, educational level, occupation, family history of diabetes, medication use, alcohol consumption, smoking history, dietary habits, and physical activity were obtained from participants using a structured interviewer-administered questionnaire.

Sample collection

A standard venepuncture method was used to obtain 8 mL of fasting venous blood from each participant after an overnight fast. Two milliliters of blood were dispensed into fluoride oxalate bottles for FPG estimation, 4 mL into K2-EDTA sample bottles for glycated hemoglobin (HbA1c), and 2 mL into plain sample bottles for biochemical assays. The blood samples in plain containers were allowed to clot and centrifuged at 3000 rpm for 5 minutes at room temperature. The sera were separated immediately into aliquots and stored at −20°C until analysis.

Determination of FPG, GGT and HbA1c

The GGT, FPG and HbA1c were determined by colorimetric methods according to Szasz (1969), Barham and Trinder (1972), and the cation-exchange resin column chromatographic method according to Trivelli *et al*. (1971), employing reagent kits obtained from Agappe Diagnostics Ltd., Kerala, India and Teco Diagnostics, USA respectively.

Determination of Serum insulin and ferritin

Serum insulin and ferritin concentration were determined using the Enzyme-Linked Immunosorbent Assay (ELISA) methods, with kits obtained from DRG International Inc., USA.

Computation of Insulin Resistance (HOMA-IR)

Insulin resistance was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) according to the formula:

$$HOMA\text{-}IR=\frac{FPG(mmol/L)\times Insulin(\mu IU/mL)}{22.5}$$

Computation of HOMA-B

Homeostatic model assessment of β-cell function (HOMA-B) was computed using the formula:

$HOMA-B=\frac{20\times Fasting\ insulin\ (\mu IU/mL)}{Fasting\ glucose\ (mmol/L)-3.5}$ (Matthews *et al*., 1985).

Computation of Ferritin:GGT ratio

Ferritin:GGT ratio was computed using the formula:

$$Ferritin{:}GGT\ Ratio=\frac{Serum\ ferritin\ (ng/mL)}{GGT\ (U/L)}$$

Computation of Disposition Index (DI)

DI = HOMA-B: HOMA-IR

Calculation of the predictive values of the evaluated indices

Positive predictive value (PPV)

$$= \frac{TP}{(TP + FP)} \times 100$$

Negative predictive value (NPV)

$$= \frac{TN}{(TN + FN)} \times 100$$

Where TP = True positive, FP = False positive, TN = True negative and FN = False negative.

Statistical analysis

Data obtained were analyzed using Statistical Package for Social Sciences (SPSS) version 27.0 (IBM Corp., Armonk, NY, USA). Results were expressed as mean ± standard deviation (SD). The normality of the data was determined by the Shapiro-Wilk test, Box and whisker plots. Student's t-test, Pearson correlation to determine association between variables. Receiver Operator Characteristic (ROC) Curve, bootstrapping, leave-one-out cross validation analyses were used to evaluate the performance of HOMA-IR, HOMA-B, DI, SF:GGT ratio in predicting β-cell dysfunction and glycemic control outcomes in T2DM. Statistical significance was set to $p \leq 0.05$.

Sample size calculation

Sample size was determined according to the method of Sullivan (2020)

$$n = \frac{\left(Z_{\alpha}+Z_{\beta}\right)^2 \cdot \bar{p}(1-\bar{p})}{(p_0 - p_1)_2}$$

- Z_{β}= Beta error at 80% power is 0.84
- Z_{α} = Z value associated with 95% confidence level is 1.96, ie, (Alpha error at 95% level of confidence)
- P_0= The anticipated probability of "exposure for people with the disease condition" (97%=0.97)
- P_1= is the proportion/anticipated probability of "exposure for people without the disease condition" 85% = 0.85 (estimated from the postulated odds ratio)
    - ṗ=mean proportion between cases and control group $(p_1+p_2)/2$ =0.97+0.86)/2=0.91

d = difference to be detected (p_0 – P1) = 0.97-0.86 = 0.11

$$n = \frac{(1.96+0.84)^2 X\ 0.91(0.09)}{(0.11)^2} = 53$$

A minimum of 53 samples is required, 50 samples used in this study is a limitation, findings require validation in a larger independent cohort.

Ethical consideration

Ethical approval was obtained from Ethics and Research Committee of the Cross River State Ministry of Health with the approval number as follows:*CRSMOH/HRP/REC/2023/470.* Informed consent was obtained from all participants. The research was conducted according to the Helsinki's declaration about research involving Human subjects (1975), and as revised subsequently.

3.0 Results

The comparison of age, blood pressure, FPG, HbA1c, BMI, GGT, ferritin, insulin (INS), HOMA-IR, HOMA-B, SF/GGT and Disposition Index (DI) between diabetic subjects and controls is shown in table 1. The SBP, FPG, HbA1c, BMI, GGT, ferritin, insulin, and HOMA-IR, were significantly higher while HOMA-B, SF/GGT and DI were significantly lower in diabetics when compared with non-diabetic controls ($p<0.05$).

The comparison of age, SBP, DBP, FPG, BMI, GGT, ferritin, INS, HOMA-IR, HOMA-B, SF/GGT and DI between diabetic subjects with good glycemic control and diabetics with poor glycemic control is shown in table 2. The FPG, INS, HOMA-IR, and SF/GGT were significantly higher while HOMA-B, BMI, and DI were significantly lower ($p<0.05$) in diabetics with HbA1c >7.2%, when compared with diabetics with HbA1c ≤ 7.2%.

The correlations among variables studied in diabetic subjects are shown in table 3. The GGT correlated positively and significantly with INS (r=0.987, p< 0.0001, 95% C.I =0.977-0.993, significant Bonferroni correction). The HOMA-IR correlated negatively with DI (partial r=-0.767, p< 0.0001, 95% C.I=-0.864--0.619, significant Bonferroni correction).

The area under the receiver operator characteristic curve of FPG, HbA1c, GGT, ferritin, insulin and

HOMA-IR among diabetic subjects is shown in figure 1. At a cutoff point of <19.96 U/L, GGT demonstrated AUC=0.941, S.E=0.026, p<0.001Gini index=0.882, max K-S =0.824, Youden's index=0.824, sensitivity=94.0%, specificity=88.4%, PPV=92.2%, NPP=90.3%, Bias-Corrected and Accelerated Bootstrap 95%C.I=0.881-0.982 and LOOCV AUC=0.932. A summary of the performance metrics of the variables is depicted in table 4.

Table 1: Comparison of age, blood pressure, FPG, HbA1c, BMI, GGT, ferritin, INS, HOMA-IR, HOMA-B, SF/GGT and DI between diabetic subjects and controls

Parameters	Diabetics (n=50)	Control (n=31)	T	p	Cohen's d	Bootstrapped BCa95%C.I
Age (yrs)	48.82 ± 7.28	47.06 ± 7.21	1.059	0.293	7.251	-1.394-5.083
SBP (mmHg)	122.46 ± 4.89	118.97 ± 2.54	3.675	<0.001*	4.157	1.984-5.236
DBP (mmHg)	75.86 ± 5.36	77.52 ± 3.79	1.501	0.137	4.825	-3.629-0.299
FPG (mmol/L)	9.26 ± 1.53	4.62 ± 0.66	15.959	<0.001*	1.272	4.133-5.215
HbA1c (%)	8.27 ± 1.70	4.23 ± 0.56	12.830	<0.001*	1.379	3.551-4.625
BMI (kg/m²)	42.62 ± 3.11	22.88 ±1.11	25.188	<0.001*	2.541	18.886-20.664
GGT (U/L)	42.50 ± 16.88	14.25 ± 3.86	9.149	<0.001*	13.506	23.360-33.652
Ferritin (ng/mL)	227.94 ± 99.64	105.20 ± 18.83	6.768	<0.001*	79.328	97.218-151.92
Insulin (µIU/mL)	15.57 ± 3.22	5.10 ± 2.07	16.137	<0.001*	2.837	9.358-11.792
HOMA-IR	3.50 ± 1.27	0.88 ± 0.21	11.401	<0.001*	1.006	2.270-3.035
HOMA-B (%)	56.69 ± 14.68	130.96 ±100.02	5.181	<0.001*	62.711	-112.035-41.90
SF/GGT	5.45 ± 1.72	7.85 ± 2.25	5.391	<0.001*	1.942	-3.267—1.47
DI	19.09 ± 9.83	177.63 ± 174.65	6.427	<0.001*	107.902	-223.520--103.94

Key: Results expressed as mean ± SD. * = significant difference between diabetic subjects and controls. SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, BMI = body mass index, GGT = gamma-glutamyl transferase, INS=insulin, HOMA-IR = homeostatic model assessment for insulin resistance, HOMA-B = homeostatic model assessment for β-cell function, SF/GGT = ferritin to gamma-glutamyl transferase ratio, DI = Disposition Index.

Table 2: Comparison of age, blood pressure, FPG, HbA1c, BMI, GGT, ferritin, INS, HOMA-IR, HOMA-B, SF/GGT and Disposition Index (DI) between diabetics with Good Glycemic Control (GGC) (HbA1c ≤7.2%) and poor Glycemic Control (PGC) HbA1c >7.2%

Parameter	GGC (HbA1c ≤7.2%) (n=18)	PGC (HbA1c >7.2%) (n=32)	T	P	Cohen's d	BCa 95% C.I
Age (yrs)	49.67± 9.54	48.34 ± 5.76	0.613	0.543	7.324	-3.507-5.785
SBP (mmHg)	122.89 ± 5.31	122.22 ± 4.71	0.461	0.647	4.931	-1.890-3.424
DBP (mmHg)	77.61 ± 6.54	74.88 ± 4.38	1.770	0.083	5.247	-0.552-6.455
FPG (mmol/L)	7.88 ± 0.79	10.03 ± 1.28	6.451	<0.001*	1.132	2.702-1.591
BMI (kg/m²)	44.07 ± 4.01	41.80 ±2.12	2.627	0.012*	2.936	0.455-4.139
GGT (U/L)	47.51 ± 19.03	39.68 ± 15.13	1.599	0.116	16.620	-3.140-18.288
SF (ng/mL)	196.04 ± 93.92	245.89 ±99.66	1.732	0.090	97.668	-107.78-6.856
Insulin (µIU/mL)	13.77 ± 2.38	16.58 ± 3.21	3.231	0.002*	2.948	-4.382—1.319
HOMA-IR	2.35 ± 0.23	4.14 ± 1.14	6.501	<0.001*	0.933	-2.181- -1.382
HOMA-B (%)	64.78 ± 15.86	52.13 ± 11.96	3.185	0.003*	13.475	4.148-21.146
SF/GGT	4.04 ± 0.94	6.25 ± 1.54	5.519	<0.001*	1.361	2.946- -1.578
DI	28.22 ±9.03	13.95±5.69	6.862	<0.001*	7.058	9.590-18.859

Key: Results expressed as mean ± SD. * = significant difference between diabetic subjects and controls. SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, BMI = body mass index, GGT = gamma-glutamyl transferase, HOMA-IR = homeostatic model assessment for insulin resistance, HOMA-B = homeostatic model assessment for β-cell function, SF/GGT = ferritin to gamma-glutamyl transferase ratio, DI = beta-cell insulin resistance index.

Table 3: Partial Correlation Matrix (Adjusted for BMI) in diabetic subjects

Variable 1	Variable 2	Partial r	95% CI	Unadjusted p-value	Bonferroni Significant?
GGT	INS	0.987	0.977-0.993	< 0.0001	Yes *
GGT	HOMA-IR	0.992	0.986-0.996	< 0.0001	Yes *
FPG	HOMA-B	-0.730	-0.841--0.562	< 0.0001	Yes *
INS	HOMA-IR	0.995	0.991-0.997	< 0.0001	Yes *
INS	HOMA-B	0.548	0.315-0.720	< 0.0001	Yes *
INS	DI	-0.801	-0.884--0.671	< 0.0001	Yes *
HOMA-IR	DI	-0.767	-0.864--0.619	< 0.0001	Yes *

Statistically significant relationships that survive the strict Bonferroni correction (p < 0.00139) are marked with an asterisk (*), FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, BMI = body mass index, GGT = gamma-glutamyl transferase, HOMA-IR = homeostatic model assessment for insulin resistance, Disposition Index (DI

Table 4: A summary of the performance metrics of the variables studied in diabetics

Biomarker	Optimal Cutoff	AUC	SE	p-val	Gini Index	Max KS Index	Youden Index (J)	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Bootstrapped BCa 95% CI	LOO-CV AUC
FPG	>6.40	0.999	0.001	<0.001	0.998	0.980	0.980	98.0	100.0	100.0	96.9	[0.994, 1.000]	0.999
HbA1c	>5.80	1.000	0.000	<0.001	1.000	1.000	1.000	100.0	100.0	100.0	100.0	[1.000, 1.000]	1.000
GGT	<19.96	0.941	0.026	<0.001	0.882	0.824	0.824	94.0	88.4	92.2	90.3	[0.881, 0.982]	0.932
Ferritin	>125.80	0.946	0.024	<0.001	0.892	0.843	0.843	84.3	100.0	100.0	81.6	[0.890, 0.988]	0.941
Insulin	< 8.70	0.819	0.051	<0.001	0.638	0.617	0.617	93.5	68.2	80.4	88.2	[0.710, 0.912]	0.803
HOMA-IR	<58.98	0.901	0.038	<0.001	0.802	0.778	0.778	100.0	77.8	85.3	100.0	[0.815, 0.966]	0.891

FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, BMI = body mass index, GGT = gamma-glutamyl transferase, SF= serum ferritin, HOMA-IR = homeostatic model assessment for insulin resistance

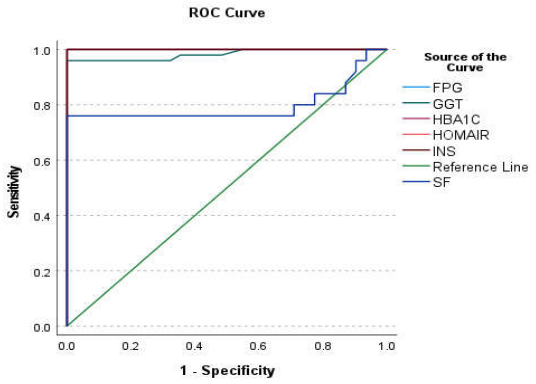

Figure 1: Receiver Operating Characteristic (ROC) Curve of FPG, HbA1c, GGT, Ferritin, Insulin, and HOMA-IR in diabetic subjects.

Discussion

The significantly higher levels of fasting plasma glucose, glycated hemoglobin, body mass index, ferritin, insulin, HOMA-IR and gamma-glutamyl transferase in diabetic subjects compared with controls may suggest persistent hyperglycemia, insulin resistance, obesity-associated inflammation and oxidative stress in diabetic subjects. This finding is similar to those of previous studies which observed significantly elevated serum ferritin levels among patients with type 2 diabetes mellitus (Fernández-Real *et al*., 2021; Wang *et al*., 2023). Similarly, previous studies reported that elevated ferritin is independently associated with metabolic syndrome, insulin resistance and increased risk of developing T2DM (Liu *et al*., 2022).

The significantly elevated gamma-glutamyl transferase observed among diabetic subjects may suggest increased oxidative stress, hepatic inflammation and altered glutathione metabolism associated with insulin resistance. This observation agrees with previous reports which demonstrated that elevated serum GGT levels are associated with insulin resistance, and type 2 diabetes mellitus (Ko *et al*., 2023). Similarly, previous studies reported that GGT may serve as a biomarker of oxidative stress (Lee *et al*., 2022). The significantly higher insulin and HOMA-IR levels observed in diabetic subjects may suggest marked insulin resistance and impaired glucose utilization in these patients. This finding is similar to that of previous studies which reported reduced β-cell function and elevated insulin resistance indices among patients with poorly controlled diabetes mellitus (Raza *et al*., 2022).

In this study diabetic subjects with good glycemic control had elevated levels of disposition index, suggesting that pancreatic beta-cells optimal functional capacity is necessary to perfectly crank out enough insulin to compensate for whatever level of insulin resistance that may be present, in subjects with good glycemic control. The elevated HOMA-IR and insulin values in subjects with poor glycemic control may indicate worsening insulin resistance resulting from chronic hyperglycemia and metabolic dysregulation. This finding agrees with previous studies which demonstrated that poor glycemic control is associated with increased oxidative stress, elevated ferritin levels and worsening insulin resistance in T2DM patients (Zhang *et al*., 2023). The significantly higher SF/GGT ratio in T2DM subjects compared with the controls may suggest a synergistic oxidative stress effect, where GGT rises in response to oxidative stress, while ferritin reflects both tissue iron stores and acute-phase inflammation. An elevated SF/GGT ratio implies a compounding toxic feedback loop, where excess iron (ferritin) drives hydroxyl radical generation via the Fenton reaction, while cellular redox defense mechanisms are overwhelmed, prompting a rise in GGT. The elevated ratio serves as a potent metabolic index tracking the intersection of iron-mediated oxidative stress, hepatic steatosis, and systemic inflammation, distinguishing a diabetic metabolic profile deeply reinforced by chronic tissue inflammation and subclinical iron overload. Also, serving as early predictor of beta-cell exhaustion, since pancreatic beta-cells have low native antioxidant expression. This observation is similar to previous studies which demonstrated positive associations between ferritin, GGT, insulin resistance and metabolic syndrome (Park *et al*., 2022).

After adjusting for BMI as a confounding factor and applying a strict Bonferroni correction, plasma GGT retained highly significant positive associations with fasting insulin ($r = 0.987$) and HOMA-IR ($r = 0.992$). Furthermore, powerful coherence structural associations weres observed within insulin dynamics variables, FPG with HOMA-B ($r = -0.730$), and Insulin with DI ($r = -0.801$), remaining robustly significant ($p < 0.0001$). These findings demonstrate that plasma GGT is a powerful, BMI-independent marker of metabolic dysfunction that is directly linked to insulin resistance, and not just a mere consequence of obesity. Furthermore, the robust, inverse structural associations within glucose-insulin dynamics highlight a highly coordinated system where worsening poor glycemic control and hyperinsulinemia tightly track the progressive collapse of pancreatic beta-cell function and overall disposition. The negative correlations of FPG and HbA1c against disposition index and HOMA-B suggest that both optimal beta cell function and insulin sensitivity are crucial in modulating glycemic indices and that progressive decline in pancreatic β-cell functional capacity may worsens glycemic status. These findings are similar to previous reports which demonstrated strong associations among hyperglycemia, obesity, ferritin, insulin resistance and impaired β-cell function in T2DM (Kim *et al*., 2022; Raza *et al*., 2022). Elevated SF/GGT in diabetics with poor glycemic control compared with diabetics with good glycemic control suggests a vicious cycle of glycation and iron release. Uncontrolled hyperglycemia (high HbA1c) worsens iron toxicity. High glucose levels promote the non-enzymatic glycation of transferrin and ferritin, reducing their iron-binding affinity. This leads to an increased loosely bound free iron, triggering extensive lipid peroxidation. Hyperglycemia and its byproduct, Advanced Glycation End-products (AGEs), provoke a profound pro-inflammatory cytokine response (e.g., TNF-alpha, IL-6). This upregulates the hepatic synthesis of ferritin as an acute-phase reactant, driving the ratio higher as glycemic control degrades. An escalated SF/GGT ratio directly mirrors the cumulative tissue-level impact of poor control, scaling linearly with HOMA-IR values. In patients with poor glycemic control, a spike in this ratio is significantly associated with an increased risk of chronic diabetic complications, particularly diabetic retinopathy, microalbuminuria, and coronary heart disease, due to widespread endothelial damage from systemic oxidative stress, serving as a predictive metric for micro/macrovascular complications. This finding is similar to that of a previous study by Lv *et al.,* (2026), which observed a non-linear association between ferritin and diabetic retinopathy.

The area under the receiver operator characteristic curve demonstrated excellent diagnostic and predictive performance for fasting plasma glucose, HbA1c, insulin and HOMA-IR, while ferritin and GGT also demonstrated good predictive and diagnostic screen utility. The close ties between actual AUC and LOOcvAUC demonstrate the robustness of the models. The good sensitivity and specificity observed for GGT and ferritin suggest that these biomarkers may provide clinically useful information regarding oxidative stress status and pancreatic β-cell deterioration in diabetic patients.

Limitations

This study has its limitations. The relatively small sample size may limit generalization of the findings to the wider diabetic population. In addition, direct oxidative stress markers and inflammatory cytokines were not evaluated which may have provided further mechanistic insights into the metabolic abnormalities observed in diabetic subjects. T2DM subjects with NAFLD were not excluded.

Conclusion

The findings of this study suggest that type 2 diabetic subjects have elevated levels of ferritin, gamma-glutamyl transferase, and reduce HOMA-B and disposition index. Good glycemic control may be associated with higher disposition index. The interaction between ferritin and GGT may serve as a significantly stronger predictor and diagnostic screen for longitudinal HOMA-B decline than either biomarker evaluated independently

Conflict of interest

The authors declare that they have no conflict of interest.

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