



Research Article

Ferroptosis-Associated Iron and Lipid Biomarkers in Early Diabetic Kidney Disease in Adults with Type 2 Diabetes Mellitus

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ABSTRACT

Diabetic kidney disease (DKD) is detected late by conventional markers such as serum creatinine and microalbuminuria. Ferroptosis has been proposed as an early contributor to diabetic renal injury; this study examined iron-status and lipid parameters as indirect, hypothesis-generating correlates. We evaluated serum ferritin, transferrin, TIBC, transferrin saturation (TSAT), and fasting lipids in 180 adults at UITH, Ilorin, Nigeria: 60 with type 2 diabetes (T2DM) and early DKD, 60 with T2DM and preserved renal function, and 60 healthy controls. Ferritin and transferrin were higher, and TSAT lower, in both T2DM groups than controls (all $p < 0.0001$); TIBC and TSAT were additionally lower in early DKD than in T2DM without DKD (TIBC: 12.2 vs 17.7 $\mu\text{mol/L}$, $p < 0.0001$; TSAT: 18.0% vs 25.0%, $p < 0.0001$), with every early-DKD TSAT value below every no-DKD value. LDL-C rose progressively across all three groups (all pairwise $p < 0.002$); triglycerides and glucose were higher, and HDL-C lower, in both diabetic groups than controls (all $p < 0.0001$). Among T2DM patients, ferritin and TIBC correlated with lipid/glycaemic indices (most FDR-adjusted $q < 0.01$); TSAT did not, beyond a borderline, FDR-non-significant link with triglycerides. In univariable, log-transformed, standardised logistic regression, lower TSAT and TIBC were associated with early DKD; TSAT showed complete separation between the two T2DM groups, requiring Firth's method (OR 0.006, 95% CI 0.001–0.054, $p < 0.0001$), while TIBC showed a conventional association (OR 0.27, 95% CI 0.14–0.55, $p = 0.0003$); ferritin's association attenuated after log-transformation ($p = 0.18$). No confounder adjustment was performed. TSAT's near-complete separation is a striking signal warranting prospective, multi-centre replication before diagnostic use.

Keywords: Diabetic kidney disease; Ferroptosis; Lipid profile; Serum ferritin; Total iron-binding capacity; Transferrin saturation; Type 2 diabetes mellitus

Citation: Olawumi, O.O., Opalekundu, A.B., Ogunwale, K.A.T., Musa, I.O., & Hassan, S.O. (2026). Ferroptosis-Associated Iron and Lipid Biomarkers in Early Diabetic Kidney Disease in Adults with Type 2 Diabetes Mellitus. *Sahel Journal of Life Sciences FUDMA*, 4(3): 235-241. DOI: <https://doi.org/10.33003/sajols-2026-0403-24>

INTRODUCTION

Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease and end-stage renal disease worldwide, arising from sustained hyperglycaemia in both type 1 and type 2 diabetes mellitus (T2DM) (Tuttle *et al.*, 2014; Kidney Disease: Improving Global

Outcomes [KDIGO] CKD Work Group, 2024). Global diabetes prevalence was estimated at 537 million adults in 2021, with sub-Saharan Africa carrying a rapidly rising share of this burden (International Diabetes Federation, 2021); in Nigeria, systematic review and meta-analysis places the pooled

prevalence of DKD among T2DM patients attending tertiary hospitals in a range that makes it one of the most consequential diabetes complications encountered in routine clinical practice (Azeez *et al.*, 2021). Despite this burden, the biochemical tools used to detect DKD remain blunt: serum creatinine does not rise meaningfully until roughly half of nephron mass is already lost, owing to compensatory hyperfiltration in surviving nephrons (Umanath & Lewis, 2018), while a substantial subset of patients develop progressive glomerular filtration rate (GFR) decline without significant albuminuria, a pattern now recognised as non-albuminuric DKD that escapes the conventional creatinine-and-albuminuria screening algorithm entirely (Shi *et al.*, 2022).

Ferroptosis is a regulated, non-apoptotic form of cell death driven by iron-catalysed, unrestrained peroxidation of polyunsaturated fatty acids within membrane phospholipids, morphologically distinct from apoptosis and dependent on an expanded labile iron pool, depleted glutathione peroxidase 4 activity, and an adequate polyunsaturated-lipid substrate (Jiang *et al.*, 2021). Renal proximal tubular cells are particularly vulnerable to this pathway under hyperglycaemic conditions, and ferroptosis has been proposed, principally on the basis of animal and cell-culture models, as a mechanistically active, potentially early contributor to diabetic renal injury, upstream of the structural damage that conventional histological and functional markers detect (Mengstie *et al.*, 2023); this remains established mechanistic evidence at the bench rather than a demonstrated clinical process in patients, and the present study tests only its indirect biochemical correlates in humans. The upstream drivers of ferroptosis, principally the size of the labile iron pool and the availability of peroxidisable lipid substrate, are in principle approximable, though not directly measured, from routine iron-status and lipid-profile assays: elevated serum ferritin has been reported to predict incident T2DM independently of adiposity (Chen *et al.*, 2018), and insulin resistance itself is thought to impair ferroportin-mediated iron export from enterocytes and macrophages, expanding intracellular and, indirectly, the circulating labile iron pool (Miao *et al.*, 2023). The atherogenic dyslipidaemia that accompanies T2DM, characterised by elevated triglycerides and reduced HDL-C, is well established in its own right (Mooradian, 2009; American Diabetes Association Professional Practice Committee, 2025) and is hypothesised, though not directly demonstrated here, to further enlarge the pool of oxidisable polyunsaturated lipid available for

ferroptotic peroxidation; the present study measures only a routine fasting lipid profile and does not assess membrane phospholipid polyunsaturated-fatty-acid composition or lipid peroxidation directly.

Serum ferritin, transferrin, total iron-binding capacity (TIBC), and a fasting lipid profile are all measurable on chemistry analysers already in routine use, so any biomarker signal identified from these parameters would be immediately actionable in a Nigerian tertiary-hospital setting without new capital investment (Uloko *et al.*, 2018). Locally generated data are particularly needed given that dietary, genetic, and inflammatory factors relevant to iron handling and lipid metabolism plausibly differ from the largely Asian, European, and North American populations in which most existing ferroptosis-biomarker data have been generated, and direct experimental ferroptosis data specific to Nigerian or wider West African T2DM populations remain limited (Oluyombo *et al.*, 2014). This study therefore evaluated serum ferritin, transferrin, TIBC, and fasting lipid profile among T2DM patients with early DKD, T2DM patients with preserved renal function, and healthy controls attending a Nigerian teaching hospital, to test the hypothesis that these ferroptosis-associated biochemical parameters would differ between groups and correlate with one another in a pattern consistent with, though not proof of, a shared, ferroptosis-permissive biochemical environment; iron status and lipid profile were evaluated as indirect, hypothesis-generating correlates of this putative pathway rather than as direct evidence of a ferroptotic process.

MATERIALS AND METHODS

Study Design and Area

A hospital-based, cross-sectional, analytical study (Setia, 2016), conducted using biochemical data collected from participants attending the Diabetic Outpatient Clinic and Medical Outpatient Department of the University of Ilorin Teaching Hospital (UIITH), Ilorin, Kwara State, Nigeria. We studied three groups of adult participants: T2DM patients with early DKD, T2DM patients with preserved renal function and no albuminuria, and apparently healthy, age- and sex-matched volunteers with no known chronic disease. T2DM diagnosis followed World Health Organization criteria. Early DKD was defined, per current KDIGO practice guidance, as an eGFR (CKD-EPI 2021 creatinine equation) in the normal-to-mildly-reduced range (≥ 60 mL/min/1.73m²) together with moderately increased albuminuria (urinary albumin-to-creatinine ratio 30–

300 mg/g, confirmed and not attributable to another identifiable cause of kidney disease), while T2DM patients without DKD had a normal albumin-to-creatinine ratio (<30 mg/g) and eGFR ≥ 60 mL/min/1.73m² (KDIGO CKD Work Group, 2024). Exclusion criteria included type 1 or secondary diabetes, known primary iron-overload disorders, established stage 3–5 chronic kidney disease at enrolment, current iron supplementation or erythropoiesis-stimulating agents, and current lipid-lowering therapy.

Ethical Considerations

Ethical approval was sought from the Kwara State Ministry of Health Ethical Review Committee, Ilorin (UITH/CAT/189/21B/792), and the study was conducted in accordance with the Nigerian National Code of Health Research Ethics and the Declaration of Helsinki (World Medical Association, 2013). Written informed consent was obtained from all participants prior to participation in the study.

Study Participants

A total of 180 participants were analyzed: 60 T2DM patients with early DKD, 60 T2DM patients without DKD, and 60 healthy controls, recruited by non-probability purposive sampling from eligible clinic attendees and, for the control group, from hospital staff, student volunteers, and companions of outpatients not themselves seeking care. Sample size was calculated using Cochran's formula, $n = Z^2p(1-p)/d^2$, based on a locally reported DKD prevalence estimate among Nigerian T2DM outpatients (Azeez *et al.*, 2021) at the conventional 95% confidence level, with an approximately even three-way split adopted across the three groups a priori to support between-group comparisons. Controls were broadly age- and sex-matched to the diabetic groups by recruitment from the same hospital catchment population.

Sample Collection and Laboratory Analysis

Venous blood was collected after an overnight fast of at least eight hours. Serum ferritin was measured by sandwich enzyme-linked immunosorbent assay (AccuBind ELISA kit, Monobind Inc., Lake Forest, California, USA); serum transferrin and total iron-binding capacity (TIBC) were each measured by sandwich enzyme-linked immunosorbent assay (Eldere ELISA kits, Shanghai Ideal Medical Technology Co., Ltd., Shanghai, China); serum iron was measured by a direct colorimetric method (Agappe Diagnostics, Kerala, India); and fasting total cholesterol (TC), triglycerides (TG), and HDL-cholesterol (HDL-C) were measured by enzymatic colorimetric methods on an automated chemistry analyzer (Agappe Diagnostics), with LDL-cholesterol (LDL-C) calculated using the

Friedewald equation. All kits were used according to the manufacturers' instructions, with routine internal quality control run alongside each analytical batch. Percentage transferrin saturation (TSAT) was calculated as serum iron ($\mu\text{mol/L}$) divided by TIBC ($\mu\text{mol/L}$), multiplied by 100.

Data Analysis

Data were analyzed using IBM SPSS Statistics, version 27.0. Group differences across the three study groups were assessed using the Kruskal-Wallis H test, with epsilon-squared (ϵ^2) as the effect-size measure and Bonferroni-corrected pairwise Mann-Whitney U tests for post-hoc comparisons. Spearman's rank correlation assessed associations between iron and lipid/glycaemic parameters among T2DM patients.. Univariable binary logistic regression was used to evaluate unadjusted associations with early DKD; Firth's penalized-likelihood method was used for TSAT because of complete separation between groups. Statistical significance was set at $p < 0.05$.

RESULTS

Fasting lipid profile and glucose differed significantly across the three study groups (Table 1). Fasting blood sugar was markedly higher in both T2DM groups than controls ($p < 0.0001$ for both) and did not differ significantly between them. Triglycerides were higher in both T2DM groups than controls ($p < 0.0001$ for both) and did not differ between the two T2DM groups. Total cholesterol was higher in both T2DM groups than controls ($p < 0.0001$ for both) and did not differ significantly between the two T2DM groups ($p = 0.061$). HDL-C was lower in both T2DM groups than controls ($p < 0.0001$ for both) and did not differ between them. LDL-C rose progressively across all three groups and differed significantly at every pairwise comparison (controls vs T2DM without DKD, $p = 0.0017$; controls vs T2DM with early DKD, $p < 0.0001$; T2DM without DKD vs T2DM with early DKD, $p = 0.0072$).

Iron-metabolism parameters also differed markedly across the three groups (Table 2). Serum ferritin was higher in both T2DM groups than in healthy controls (T2DM without DKD: median 157.5 [IQR 88.0–242.5] ng/mL; T2DM with early DKD: 192.2 [99.7–384.9] ng/mL; healthy controls: 31.5 [15.8–48.5] ng/mL), but did not differ significantly between the two T2DM groups ($p = 0.138$). TIBC was similar between healthy controls and T2DM without DKD (18.4 [12.3–22.2] vs 17.7 [15.1–20.2] $\mu\text{mol/L}$, $p = 0.578$) but was substantially lower in T2DM with early DKD (12.2 [7.5–13.8] $\mu\text{mol/L}$; $p = 0.0002$ vs controls, $p < 0.0001$ vs T2DM without DKD). Serum transferrin was likewise

higher in both T2DM groups than controls ($p < 0.0001$ for both) but did not differ significantly between them ($p = 0.998$). With serum iron now measured directly, standard percentage transferrin saturation fell progressively and sharply across the three groups (healthy controls 33.0% [33.0–34.0]; T2DM without DKD 25.0% [25.0–26.0]; T2DM with early DKD 18.0% [17.1–18.0]), with every pairwise comparison

significant (all $p < 0.0001$). Notably, the T2DM-without-DKD and T2DM-with-early-DKD distributions did not overlap at all, every early-DKD TSAT value was below every no-DKD value giving TSAT the largest effect size of any parameter examined in this study ($\epsilon^2 = 0.890$, versus 0.154 for TIBC and 0.566 for ferritin).

Table 1: Fasting Lipid Profile and Blood Glucose across the Three Study Groups

Parameter	Healthy Control (n=60)	T2DM without DKD (n=60)	T2DM with early DKD (n=60)	H	p	ϵ^2
FBS (mmol/L)	4.8 (4.1–5.2) ^a	8.4 (6.9–9.9) ^b	8.0 (6.1–11.0) ^b	99.83	< 0.0001	0.553
TC (mmol/L)	4.0 (3.1–4.9) ^a	5.1 (4.1–6.0) ^b	5.2 (4.9–5.9) ^b	42.68	< 0.0001	0.230
TG (mmol/L)	1.2 (1.0–1.6) ^a	2.0 (1.5–2.5) ^b	1.9 (1.2–2.5) ^b	37.86	< 0.0001	0.203
HDL-C (mmol/L)	1.30 (1.10–1.43) ^b	1.00 (0.88–1.30) ^a	0.95 (0.68–1.20) ^a	27.04	< 0.0001	0.141
LDL-C (mmol/L)	2.35 (2.10–2.60) ^a	3.00 (2.00–4.03) ^b	3.40 (3.00–4.00) ^c	60.18	< 0.0001	0.329

Within a row, values sharing a superscript letter did not differ significantly on Bonferroni-corrected pairwise Mann-Whitney U post-hoc comparison ($p > 0.05$); values with no shared letter differed significantly ($p < 0.05$). H = Kruskal-Wallis test statistic; ϵ^2 = epsilon-squared effect size.

Table 2: Iron-Metabolism Parameters Across the Three Study Groups

Parameter	Healthy Control (n=60)	T2DM without DKD (n=60)	T2DM with early DKD (n=60)	H	P	ϵ^2
Ferritin (ng/mL)	31.5 (15.8–48.5) ^a	157.5 (88.0–242.5) ^b	192.2 (99.7–384.9) ^b	102.25	< 0.0001	0.566
Transferrin (g/L)	0.55 (0.38–0.70) ^a	1.20 (0.98–1.53) ^b	1.20 (0.90–1.70) ^b	89.07	< 0.0001	0.492
TIBC (μmol/L)	18.4 (12.3–22.2) ^b	17.7 (15.1–20.2) ^b	12.2 (7.5–13.8) ^a	29.27	< 0.0001	0.154
TSAT (%)	33.0 (33.0–34.0) ^c	25.0 (25.0–26.0) ^b	18.0 (17.1–18.0) ^a	159.62	< 0.0001	0.890

Values sharing a superscript letter did not differ significantly on Bonferroni-corrected pairwise Mann-Whitney U post-hoc comparison ($p > 0.05$); values with no shared letter differed significantly ($p < 0.05$). H = Kruskal-Wallis test statistic; ϵ^2 = epsilon-squared effect size. TIBC = total iron-binding capacity; TSAT = percentage transferrin saturation, T2DM = type 2 diabetes mellitus; DKD = diabetic kidney disease.

Among T2DM patients (early DKD and no-DKD groups combined, $n = 120$), ferritin correlated positively with total cholesterol ($r = 0.46$, $p < 0.0001$, $q < 0.0001$), triglycerides ($r = 0.50$, $p < 0.0001$, $q < 0.0001$), LDL-C ($r = 0.37$, $p < 0.0001$, $q < 0.0001$), and fasting blood sugar ($r = 0.38$, $p < 0.0001$, $q < 0.0001$), and negatively with HDL-C ($r = -0.39$, $p < 0.0001$, $q < 0.0001$). TIBC correlated negatively with total cholesterol ($r = -0.39$, $p < 0.0001$, $q < 0.0001$) and LDL-C ($r = -0.44$, $p < 0.0001$, $q < 0.0001$), and positively with HDL-C ($r = 0.26$, $p = 0.0045$, $q = 0.0085$), but not significantly with triglycerides or fasting blood sugar after correction (both $q > 0.5$). TSAT, by contrast, correlated only weakly and inconsistently with the lipid/glycaemic panel: a nominal association with triglycerides ($r = 0.18$, $p = 0.044$) did not survive false-discovery-rate correction ($q = 0.074$), and TSAT showed no association with total cholesterol, HDL-C, LDL-C, or fasting blood sugar (all $q > 0.5$) (Table 3). This pattern indicates that TSAT's strong discrimination of early DKD (Table 2, Figure 1) is largely independent of the atherogenic-lipid signal carried by ferritin and TIBC.

T2DM patients with early DKD and without DKD combined ($n = 120$). r = Spearman rank correlation coefficient; q = Benjamini-Hochberg false-discovery-rate-adjusted p -value across the 15 correlations shown in this table. TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; FBS = fasting blood sugar; TSAT = percentage transferrin saturation; TIBC = total iron-binding capacity.

In univariable logistic regression comparing T2DM patients with early DKD against T2DM patients without DKD, lower TSAT and lower TIBC were strongly associated with early-DKD status in this unadjusted analysis. For TSAT, every early-DKD value fell below every no-DKD value. Firth's penalized-likelihood method was used instead, giving OR 0.006 (95% CI 0.001–0.054, $p < 0.0001$) per one-standard-deviation increase in log-transformed TSAT. TIBC showed a more conventional association (OR 0.27, 95% CI 0.14–0.55, $p = 0.0003$) per one-standard-deviation increase in log-transformed TIBC. The corresponding association for log-transformed

ferritin was in the same direction but did not reach statistical significance (OR 1.28, 95% CI 0.89–1.85, $p=0.183$), in contrast to a nominally significant association observed when ferritin was modelled on its untransformed scale (OR 1.77, 95% CI 1.15–2.72,

$p=0.0098$), indicating that ferritin's raw-scale signal was disproportionately driven by a small number of markedly elevated individual values rather than a consistent shift across the whole distribution (Figure 1).

Table 3: Spearman Correlations between Iron-Metabolism Parameters and Lipid/Glycaemic Indices Among T2DM Patients (n = 120)

Iron parameter	TC	TG	HDL-C	LDL-C	FBS
Ferritin	$r=0.46$, $p<0.0001$, $q<0.0001$	$r=0.50$, $p<0.0001$, $q<0.0001$	$r=-0.39$, $p<0.0001$, $q<0.0001$	$r=0.37$, $p<0.0001$, $q<0.0001$	$r=0.38$, $p<0.0001$, $q<0.0001$
TSAT	$r=0.01$, $p=0.879$, $q=0.879$	$r=0.18$, $p=0.044$, $q=0.074$	$r=0.02$, $p=0.860$, $q=0.879$	$r=-0.05$, $p=0.555$, $q=0.640$	$r=0.08$, $p=0.406$, $q=0.508$
TIBC	$r=-0.39$, $p<0.0001$, $q<0.0001$	$r=-0.08$, $p=0.377$, $q=0.508$	$r=0.26$, $p=0.0045$, $q=0.0085$	$r=-0.44$, $p<0.0001$, $q<0.0001$	$r=-0.09$, $p=0.342$, $q=0.508$

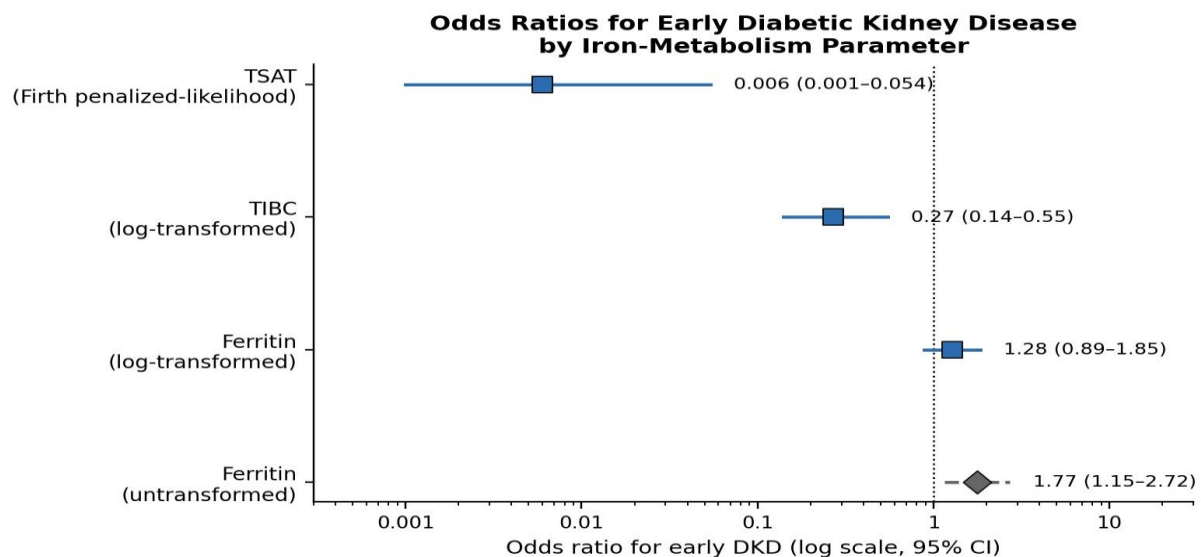


Figure 1: Odds Ratios for Early Diabetic Kidney Disease by Iron-Metabolism Parameter

Univariable logistic regression, T2DM patients with early DKD versus T2DM patients without DKD (n = 120). Squares/blue lines: odds ratio (95% CI) per one-standard-deviation increase in the log-transformed. Diamond/grey dashed line: the corresponding odds ratio for ferritin modelled on its untransformed, standardised scale (contrast only). Vertical dotted line marks no association (OR = 1); DKD = diabetic kidney disease; TSAT = percentage transferrin saturation; TIBC = total iron-binding capacity

DISCUSSION

This study evaluated ferroptosis-associated iron-metabolism parameters and fasting lipid profile as early biochemical indicators of DKD in T2DM patients. Two findings stand out. First, both T2DM groups, irrespective of renal status, showed higher ferritin and lower TSAT, and higher triglycerides and LDL-C and lower HDL-C, than healthy controls, consistent with the broader literature linking elevated ferritin to incident T2DM and impaired insulin-mediated ferroportin function (Chen *et al.*, 2018; Miao *et al.*, 2023) and linking atherogenic dyslipidaemia to the diabetic state itself (Mooradian, 2009; American

Diabetes Association Professional Practice Committee, 2025), rather than specifically to renal involvement. Second, and considerably more striking, TSAT and TIBC further distinguished T2DM patients with early DKD from those with preserved renal function in this unadjusted analysis, with TSAT showing complete, non-overlapping separation between the two T2DM groups, whereas ferritin did not discriminate the two T2DM groups, this pattern is presented here as an observed association rather than a demonstrated mechanistic conclusion.

The progressive falls in TIBC and TSAT from healthy controls through T2DM without DKD to T2DM with

early DKD are compatible with several, non-mutually-exclusive explanations that this cross-sectional design cannot distinguish: reduced hepatic transferrin synthesis, chronic low-grade inflammation, altered nutritional or obesity/metabolic status, or a genuine expansion of the iron-transport compartment as renal function declines. We present the shared, ferroptosis-permissive biochemical environment framing as one plausible interpretation of this pattern, not as a demonstrated finding. The completeness of the separation in TSAT between the two T2DM groups is, on its own terms, an unusually clean signal for a real-world clinical biomarker, but could equally be shaped by the modest sample size (60 per group), the single-centre setting, or unmeasured selection factors related to the non-probability sampling used; independent, multi-centre, prospective replication is needed before this separation is treated as a reliable or generalisable finding, and it should not by itself be read as evidence that TSAT can distinguish early DKD from T2DM without DKD at the individual-patient level in unselected populations. That ferritin itself did not discriminate early DKD from T2DM without DKD, despite being higher in both relative to controls, argues against ferritin as a stand-alone early-DKD marker in this population and instead points toward TIBC and TSAT as the more informative parameters within the iron-status panel examined here.

The correlations between ferritin and an atherogenic lipid profile (higher triglycerides, LDL-C, and fasting glucose, lower HDL-C) among T2DM patients are consistent with the hypothesis that iron loading and lipid substrate availability move together in this population; we present this as a plausible biological interpretation rather than direct evidence of a shared, ferroptosis-permissive pathway, since no marker of lipid peroxidation or membrane phospholipid composition was measured. TIBC showed a similar, though somewhat weaker, correlation pattern with the lipid profile. TSAT, by contrast, correlated only weakly and inconsistently with lipid and glycaemic indices, indicating that its strong discrimination of early-DKD status is largely independent of the atherogenic-lipid signal captured by ferritin and TIBC, and may reflect a distinct aspect of iron handling in this population. These findings should be interpreted against the persistent limitation of conventional DKD screening: creatinine-based estimates do not detect injury until substantial nephron loss has occurred (Umanath & Lewis, 2018), and a meaningful proportion of patients with progressive GFR decline never develop significant

albuminuria (Shi *et al.*, 2022), so biochemical parameters that might shift earlier than glomerular filtration, such as TIBC and TSAT, merit further prospective, confounder-adjusted, multi-centre evaluation as adjuncts to, rather than replacements for, existing screening tools; the present findings, notwithstanding the striking TSAT separation observed, do not support any change to current DKD screening practice on their own.

CONCLUSION

TIBC and TSAT, but not ferritin alone, distinguished T2DM patients with early DKD from those with preserved renal function, with TSAT showing complete, non-overlapping separation between the two T2DM groups. Ferritin and TIBC also correlated with an atherogenic lipid profile, consistent with, but not proof of, a shared ferroptosis-permissive environment. As all associations are unadjusted and no ferroptosis-specific marker was measured, these findings are hypothesis-generating; TSAT and TIBC warrant prospective, multi-centre validation before any diagnostic use is considered.

Author Contributions: Oluwatoni Olabimpe Olawumi conceived the study, designed the methodology, and did biochemical analyses. Ahmmed Bayo Opalekundu served as the main supervisor of the study. Ogunwale Kolawole Ayobami Tajudeen and Ibrahim Olayinka Musa assisted with the biochemical analyses. Seidat Omolabake Hassan performed the statistical analysis and did manuscript writing and review. All authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

Funding: The research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Data Availability: The dataset analysed during the current study is available from the corresponding author on reasonable request.

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