

Plasma Proteomics Reveals Ferroptosis-Associated Signatures in Obesity and Type 2 Diabetes

Rui Vitorino

`rvitorino@ua.pt`

University of Aveiro

Hilde Halland

Haukeland University Hospital

Helga Midtbø

Haukeland University Hospital

Klaus Meyer

Bevital

Georgios Kararigas

University of Nicosia, UNIC Athens

Eva Gerdt

Haukeland University Hospital

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Abstract

Background

Ferroptosis is an iron-dependent form of regulated cell death driven by lipid peroxidation and redox imbalance. Obesity and type 2 diabetes mellitus (T2DM) are characterized by chronic inflammation, insulin resistance, oxidative stress, and disrupted lipid and iron homeostasis, which may promote ferroptosis.

Objective

Ferroptosis-associated molecular signatures have not been systematically evaluated in large human cohorts.

Methods

Plasma proteomics was performed in 450 participants in the FAT-associated Cardiovascular dysfunction (FATCOR) cohort (body mass index [BMI] >27 kg/m²) using the Olink® Target 96 Inflammation panel. Associations between protein levels and metabolic traits (BMI, HbA_{1c}, and T2DM status) were assessed using Spearman correlation. Proteins with $|\rho| \geq 0.3$ and false discovery rate (FDR) <0.05 were subjected to functional enrichment analysis.

Results

A distinct circulating proteomic signature associated with ferroptosis-related pathways was identified across the metabolic spectrum. Redox-responsive proteins, including IL-6, CXCL9, CCL11, CDCEP1, and FGF-21, were positively associated with higher BMI and HbA_{1c}, whereas anti-inflammatory regulators, such as IL-10RB and LAP–TGF- β 1 were reduced. Glycaemic status, particularly HbA_{1c}, showed a stronger association with ferroptosis-related signatures than BMI or homeostasis model assessment of insulin resistance (HOMA-IR). Enrichment analysis demonstrated activation of pathways related to oxidative stress, iron ion homeostasis, and lipid peroxidation.

Conclusions

Metabolic dysfunction is associated with systemic activation of ferroptosis-related molecular pathways in humans. Circulating proteomic signatures may provide mechanistic insight into redox-driven tissue damage and support the development of biomarkers for cardiometabolic risk stratification.

Highlights

- Plasma proteomics characterized ferroptosis-related signatures in 450 adults.
- Glycaemic burden was more strongly linked to ferroptotic signatures than adiposity.
- HbA_{1c} outperformed BMI and HOMA-IR as a correlate of ferroptosis-associated activity.

- Type 2 diabetes was associated with a higher composite ferroptosis risk score.
- IL-6, CXCL9, CCL11, CDCP1 and FGF-21 contributed to the pro-ferroptotic profile.

Introduction

Obesity and type 2 diabetes mellitus (T2DM) are chronic metabolic disorders characterized by excessive nutrient load, mitochondrial dysfunction, and persistent low-grade inflammation. These conditions disrupt cellular redox homeostasis, leading to increased reactive oxygen species (ROS) production, impaired antioxidant defenses, and altered lipid and iron metabolism (1). Together, these disturbances create a pro-oxidative environment that exacerbates metabolic dysfunction and promotes regulated forms of cell death (2).

Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation, has emerged as a mechanistic link between metabolic stress, chronic inflammation, and tissue dysfunction(3). It is characterized by the accumulation of phospholipid hydroperoxides, depletion of glutathione (GSH), inactivation of glutathione peroxidase-4 (GPX4), and dysfunction of the cystine/glutamate antiporter system Xc⁻. These processes, including iron-catalyzed Fenton reactions, dysregulated polyunsaturated fatty acid (PUFA) metabolism, and impaired antioxidant capacity, closely mirror the redox phenotype observed in obesity and T2DM [3,4].

Increasing evidence indicates that metabolic tissues in obesity and T2DM, including adipose tissue, liver, kidney, and endothelium, are exposed to ferroptotic stress driven by ROS accumulation, mitochondrial overload, and inflammation-mediated iron dysregulation. Hyperglycaemia and dyslipidaemia accelerate lipid peroxidation, while inflammatory signalling pathways impair antioxidant responses, lowering the threshold for ferroptotic damage (4–6). Ferroptosis has been implicated in multiple cardiometabolic complications, including diabetic nephropathy, hepatic steatosis, and endothelial dysfunction, highlighting its potential relevance in human disease (7). Recently, ferroptosis has emerged as a novel pathophysiological mechanism in cardiovascular disease, in particular heart failure (3, 8).

Despite these advances, clinical evidence of ferroptosis-associated molecular signatures in humans remains limited, as current knowledge is largely derived from experimental models. Plasma proteins related to inflammation, oxidative stress, iron homeostasis, and lipid metabolism may serve as accessible surrogates of ferroptosis-related processes; however, their coordinated behaviour in human metabolic disease has not been systematically characterized (9). In particular, exploration in patient cohorts with obesity or T2DM is relevant, since these conditions represent precursors of heart failure (10, 11). Therefore, this study aimed to identify circulating proteomic signatures associated with ferroptosis in obesity and T2DM, and to determine whether systemic metabolic dysfunction is linked to pathways related to oxidative stress, iron homeostasis, and lipid peroxidation in a well-characterized human cohort.

Material and Methods

Study Cohort

This study was conducted within the FAT-associated Cardiovascular dysfunction (FATCOR)(12) study, a well-characterized human cohort comprising 450 adults (aged 30–65 years) with body mass index (BMI) > 27 kg/m² (13–15). All participants were free from clinically diagnosed cardiovascular disease at enrollment.(13, 14)

Participants were classified according to obesity and type 2 diabetes mellitus (T2DM) status. Obesity was defined as BMI ≥ 30 kg/m². T2DM was defined based on established clinical criteria (HbA_{1c} ≥6.5% or fasting plasma glucose ≥ 7.0 mmol/L). These classifications were used for group comparisons and correlation analyses.

Clinical and Anthropometric Data Collection

Standardized measurements were obtained for height, weight, systolic and diastolic blood pressure (SBP and DBP), and heart rate. BMI was calculated as weight (kg) divided by height squared (m²). Fasting blood samples were collected and analyzed using certified clinical laboratory methods for glucose, insulin, C-peptide, HbA1c, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, and creatinine. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR), calculated as fasting glucose (mmol/L) × fasting insulin (μU/mL) / 22.5. Estimated glomerular filtration rate was calculated from serum creatinine using the CKD-EPI Eq. (16).

Proteomic Profiling, Data Preprocessing and Statistical Analysis

Statistical analyses were performed using R. Clinical and biochemical variables were checked for consistency, missing values, and biologically implausible entries before analysis. The corrected creatinine and estimated glomerular filtration rate (eGFR) variables were merged into the analytical dataset using FATCOR ID and used for the final descriptive statistics. Creatinine values were converted to mg/dL where required, and eGFR was reported as mL/min/1.73 m². Plasma protein abundance was analysed using normalized protein expression (NPX) values on a log₂ scale. Proteins with more than 20% of values below the limit of detection were excluded from downstream analyses. No imputation of missing proteomic values was performed. Only proteins passing quality-control and detection thresholds were retained. Continuous variables are presented as mean ± standard deviation or median with interquartile range, depending on distribution. Categorical variables are presented as counts and percentages. Between-group comparisons were performed according to obesity status and type 2 diabetes mellitus (T2DM) status using Student's t-test or the Mann–Whitney U test for continuous variables, and the χ² test or Fisher's exact test for categorical variables, as appropriate.

Associations between clinical variables and circulating protein levels were assessed using Spearman rank correlation analysis. The main metabolic variables of interest were body mass index (BMI), glycated haemoglobin (HbA1c), and T2DM status. Secondary analyses were performed using fasting glucose, fasting insulin, fasting C-peptide, HOMA-IR, and oral glucose tolerance test (OGTT)-derived glucose and insulin measurements. HOMA-IR was calculated as fasting glucose (mmol/L) $\times$ fasting insulin (μ U/mL) / 22.5. Proteins showing significant associations with metabolic traits were selected using an absolute Spearman correlation coefficient of $|r| \geq 0.3$ and a false discovery rate (FDR) < 0.05 . Multiple testing correction was performed using the Benjamini–Hochberg method. These proteins were subsequently used for functional enrichment analysis and for construction of the ferroptosis-associated proteomic score. Significantly associated proteins were subjected to over-representation analysis using Gene Ontology (GO) and KEGG pathway databases to identify biological processes related to oxidative stress, iron homeostasis, and lipid peroxidation.

Ferroptosis Risk Score Construction

To quantify systemic ferroptosis-associated molecular activity, a composite ferroptosis risk score was derived from circulating proteins significantly associated with metabolic traits ($|r| \geq 0.3$, FDR < 0.05). The score was constructed by aggregating normalized protein expression (NPX, log2 scale) of proteins positively associated with oxidative stress, inflammation, lipid peroxidation, and subtracting proteins with inverse associations reflecting anti-inflammatory or regulatory pathways.

This approach is consistent with previously established composite biomarker and pathway activity scoring strategies, in which standardized expression values are combined to reflect coordinated biological processes at the system level (17, 18).

For each participant, the ferroptosis risk score represents the standardized sum of pro-ferroptotic signals minus anti-ferroptotic signals, providing an integrated measure of systemic ferroptotic susceptibility.

Results

Cohort Characteristics and Metabolic Stratification

The study included 450 participants from the FATCOR cohort, of whom were female 262 (58.2%) were obese (Table 1). The obese group had higher blood pressure, fasting glucose, HbA1c, serum triglycerides, and creatinine, lower HDL cholesterol and eGFR, and a higher prevalence of T2DM (all $p < 0.01$, where applicable) (Table 1). Within the cohort, individuals were stratified according to obesity and T2DM status.

Table 1
Clinical Characteristics of the FATCOR Cohort (n = 450)

Variable	Total Cohort	Non-Obese (BMI < 30)	Obese (BMI ≥ 30)	p-value
n (%)	450 (100%)	188 (41.8%)	262 (58.2%)	—
Age (years)	49 ± 9	48 ± 9	49 ± 9	0.22
Sex (F/M)	262 / 188	120 / 68	142 / 120	0.08
BMI (kg/m ²)	32.0 ± 4.3	28.1 ± 1.1	35.2 ± 3.9	< 0.001
Fat mass (%)	39.8 ± 7.5	34.6 ± 6.2	43.1 ± 6.3	< 0.001
Systolic BP (mmHg)	127 ± 17	123 ± 16	130 ± 17	< 0.001
Diastolic BP (mmHg)	78 ± 10	76 ± 9	80 ± 10	< 0.001
Heart rate (bpm)	72 ± 11	70 ± 11	74 ± 11	0.01
Fasting glucose (mmol/L)	5.6 ± 1.4	5.1 ± 0.7	6.0 ± 1.7	< 0.001
HbA _{1c} (%)	5.6 ± 0.9	5.3 ± 0.5	5.8 ± 1.0	< 0.001
Diabetes mellitus n (%)	82 (18.2%)	20 (10.6%)	62 (23.7%)	< 0.001
Total cholesterol (mg/dL)	199 ± 41	201 ± 40	198 ± 42	0.42
LDL-C (mg/dL)	123 ± 35	124 ± 34	122 ± 36	0.61
HDL-C (mg/dL)	49 ± 12	53 ± 13	46 ± 11	< 0.001
Triglycerides (mg/dL)	148 ± 76	132 ± 58	159 ± 85	< 0.001
Creatinine (mg/dL)	0.78 ± 0.19	0.74 ± 0.16	0.81 ± 0.20	< 0.001
eGFR (mL/min/1.73 m ²)	92 ± 13	94 ± 12	90 ± 13	0.003

Plasma Proteomic Landscape Associated with BMI and Glycemic Status

Proteomic profiling using the Olink® Target 96 Inflammation panel yielded robust quantification across the majority of targeted proteins after quality control filtering. Analyses were performed using both continuous (BMI, HbA_{1c}) and categorical (T2DM status) variables to ensure consistency with cohort stratification.

Spearman correlation analysis identified a subset of circulating proteins significantly associated with BMI and glycemic status ($|p| \geq 0.3$, FDR < 0.05). This subset of proteins was subsequently used to construct the ferroptosis risk score, with positively associated proteins contributing to the pro-ferroptotic component and inversely associated proteins contributing to the anti-ferroptotic component, as

described in Methods. These associations revealed a coordinated proteomic response linking adiposity and glucose dysregulation with inflammatory and redox-related pathways.

Among the most strongly associated proteins were IL-6, CXCL9, CCL11, CDCEP1, and FGF-21, which demonstrated consistent positive correlations with both BMI and HbA1c (Fig. 1, Fig. 2). These proteins are known mediators of inflammatory signaling, metabolic stress, and cellular responses to oxidative damage. Conversely, regulatory proteins with anti-inflammatory and immunomodulatory functions, including IL-10 receptor beta (IL-10RB) and LAP-TGF- β 1, exhibited inverse associations, suggesting attenuation of protective signaling pathways in individuals with higher metabolic burden.

Importantly, individuals with T2DM exhibited significantly higher ferroptosis risk scores compared with those without T2DM (Fig. 3), confirming that categorical disease stratification aligns with the continuous glycaemic signal. To determine whether the ferroptosis-associated proteomic signature was primarily related to chronic glycaemic exposure, estimated insulin resistance, or lifestyle-related metabolic variation, we performed secondary analyses incorporating HOMA-IR, fasting insulin, fasting C-peptide, OGTT-derived glucose and insulin measurements, and self-reported physical activity. HbA1c remained the strongest metabolic correlate of the ferroptosis-associated score, whereas fasting glucose and OGTT-derived glucose showed weaker but directionally consistent associations. In contrast, HOMA-IR and fasting insulin were not significantly associated with the ferroptosis score after correction for multiple testing. Similarly, self-reported physical activity showed no significant association with the score.

In multivariable models adjusted for age, sex, BMI, HbA1c, and log-transformed HOMA-IR, HbA1c remained independently associated with the ferroptosis-associated score, whereas HOMA-IR did not. These findings indicate that the circulating ferroptosis-related proteomic signature is more closely linked to chronic glycaemic burden than to estimated insulin resistance alone.

To determine whether the ferroptosis-associated proteomic signature was primarily related to chronic glycaemic exposure or estimated insulin resistance, we performed secondary analyses incorporating HOMA-IR, fasting insulin, fasting C-peptide, and OGTT-derived glucose and insulin measurements. HbA1c remained the strongest metabolic correlate of the ferroptosis-associated score, whereas fasting glucose and OGTT-derived glucose showed weaker but directionally consistent associations. In contrast, HOMA-IR and fasting insulin were not significantly associated with the ferroptosis score after correction for multiple testing. These findings indicate that systemic metabolic dysfunction is associated with a molecular environment permissive to ferroptotic processes.

Although obesity and T2DM shared a common inflammatory and oxidative signature, subtle differences were observed in the magnitude and pattern of protein associations (Fig. 4). Obesity was primarily associated with proteins linked to chronic low-grade inflammation and adipose tissue-driven signaling, whereas T2DM showed stronger associations with proteins involved in metabolic stress, glucose dysregulation, and redox imbalance. Despite these differences, both conditions converged on pathways

related to oxidative stress and lipid peroxidation, reinforcing a shared mechanistic axis consistent with ferroptotic priming (Fig. 5).

Circulating proteins included in the ferroptosis risk score, grouped according to their direction of association with metabolic traits. Pro-ferroptotic proteins (e.g., IL-6, CXCL9, CCL11, CDCP1, FGF-21) contribute positively, whereas anti-ferroptotic proteins (e.g., IL-10RB, LAP-TGF- β 1) contribute negatively to the composite score. Where applicable, statistical comparisons were performed using the Kruskal-Wallis test with multiple testing correction.

Scatter plot illustrating the relationship between HbA1c (%) and ferroptosis risk score, with color gradient representing magnitude of ferroptosis-associated molecular activity. Higher HbA1c levels are associated with progressively elevated ferroptosis risk scores, highlighting glycaemic dysregulation as a key driver of systemic ferroptotic priming. The regression line indicates a significant positive trend consistent with increased oxidative stress and lipid peroxidation in individuals with poor glycaemic control.

Discussion

This study provides novel evidence from the FATCOR cohort of individuals with overweight and obesity free from overt cardiovascular disease that metabolic dysfunction is associated with a systemic circulating proteomic profile enriched for ferroptosis-related molecular pathways in humans. By integrating plasma proteomics with detailed clinical phenotyping in FATCOR, we demonstrate, to our knowledge for the first time in a large human obesity-T2DM cohort, that circulating proteins linked to oxidative stress, iron homeostasis, and lipid peroxidation are significantly altered across the obesity-T2DM spectrum. Importantly, our findings indicate that glycaemic dysregulation, rather than adiposity alone, is the principal driver of this ferroptosis-associated proteomic signature. A central observation of this study is the dissociation between BMI and ferroptotic susceptibility. Despite clear associations between BMI and inflammatory mediators, the composite ferroptosis score showed no significant relationship with BMI. In contrast, HbA_{1c} exhibited a robust and highly significant positive correlation with ferroptosis-associated signatures, and individuals with T2DM demonstrated a marked shift toward a pro-ferroptotic proteomic profile. The availability of HOMA-IR and OGTT-derived variables allowed us to further distinguish chronic glycaemic exposure from estimated insulin resistance. Notably, HOMA-IR and fasting insulin were not significantly associated with the ferroptosis-associated score after correction for multiple testing, whereas HbA1c and fasting glucose showed stronger and more consistent associations. This suggests that sustained glycaemic burden, rather than insulin resistance per se, may be more closely linked to systemic ferroptotic priming in this cohort. Mechanistically, this interpretation is consistent with the role of chronic hyperglycaemia in promoting mitochondrial ROS production, advanced glycation end-product formation, antioxidant depletion, and lipid peroxidation. These findings suggest that hyperglycaemia and metabolic stress, rather than excess adiposity per se, are key determinants of systemic redox imbalance and lipid peroxidation. This distinction is mechanistically plausible, as chronic glucose exposure amplifies mitochondrial ROS production, promotes advanced

glycation end-products, and disrupts cellular antioxidant systems, thereby lowering the threshold for ferroptotic damage(19, 20).

At the molecular level, the identified protein signature reflects the convergence of the three canonical pillars of ferroptosis: oxidative stress, iron dysregulation, and lipid peroxidation. Proteins, such as IL-6, CXCL9, CCL11, CDCP1, and FGF-21, were consistently elevated in association with worsening metabolic status. These mediators are known to promote ROS generation, inflammatory amplification, and cellular stress signalling, thereby facilitating the biochemical conditions required for ferroptotic priming. This interpretation is consistent with experimental studies showing induction of FGF-21 under conditions of mitochondrial dysfunction and impaired redox homeostasis (21, 22).

Conversely, anti-inflammatory and regulatory proteins, including IL-10RB and LAP–TGF- β 1, were reduced in individuals with higher metabolic burden. The downregulation of these pathways suggests a loss of protective buffering capacity against oxidative and inflammatory stress (23, 24). From a ferroptosis perspective, this imbalance is critical, as diminished antioxidant signaling, potentially linked to impaired Nrf2 activity and reduced glutathione availability, facilitates the accumulation of lipid hydroperoxides and sensitizes cells to iron-dependent membrane damage (25, 26). Thus, the observed proteomic profile represents not only increased pro-oxidant signaling but also a concurrent failure of endogenous defense mechanisms.

Pathway enrichment analysis further supports this interpretation, demonstrating coordinated activation of biological processes related to “response to oxidative stress,” “iron ion homeostasis,” and “lipid peroxidation.” These pathways closely align with the established biochemical framework of ferroptosis, in which iron-catalyzed Fenton reactions and peroxidation of polyunsaturated fatty acids drive membrane damage and cell death (27, 28). Importantly, our findings extend these mechanistic insights from experimental systems to a human population context, suggesting that ferroptosis is not merely a cellular phenomenon but may represent a systemic feature of metabolic disease. In particular, several of the identified proteins are functionally linked to ferroptosis-relevant biological processes. Pro-inflammatory mediators, including IL-6 and CXCL9, have been associated with ROS generation and inflammatory amplification, thereby contributing to oxidative stress. FGF-21 is a metabolic stress-responsive hormone involved in lipid metabolism and adaptation to energetic imbalance, while CDCP1 has been implicated in cellular stress signalling and membrane remodelling. The convergence of these redox, inflammatory, and metabolic signals supports the presence of a ferroptosis-associated circulating proteomic profile in individuals with obesity and T2DM. These findings are compatible with a model in which ferroptosis-related molecular processes may contribute to the link between metabolic dysfunction and tissue stress; however, direct ferroptotic cell death or cellular susceptibility was not assessed in this study.

A key conceptual advance from this work is the identification of a systemic ferroptosis phenotype in metabolic dysfunction. Taken together, these findings suggest that obesity and T2DM are associated with coordinated changes in circulating proteins involved in inflammation, redox regulation, iron-related

biology, and lipid peroxidation. By combining correlation-based plasma proteomics with functional pathway enrichment, our results indicate that metabolic dysfunction is associated with a systemic shift toward ferroptosis-related molecular processes. This transition is characterized by increased oxidative stress signaling, altered inflammatory regulation, and enrichment of pathways linked to iron homeostasis and lipid peroxidation, which are key biochemical features of ferroptosis. Importantly, these data should be viewed as evidence for a circulating proteomic profile associated with ferroptosis, and not as direct evidence of ferroptotic cell death or cellular susceptibility. Therefore, the observed plasma signature is best interpreted as a systemic molecular readout compatible with ferroptotic priming in metabolic disease. In this context, persistent glycemic burden may create a pro-oxidative, lipid peroxidation-prone environment, potentially linking metabolic dysregulation to tissue stress and cardiometabolic complications. Rather than reflecting isolated tissue-specific processes, the circulating proteomic signature indicates that ferroptosis-related pathways are coordinately dysregulated at the organismal level. This may help explain the multi-organ nature of cardiometabolic complications, including nephropathy, hepatic steatosis, and vascular dysfunction, where oxidative stress and lipid peroxidation play central roles (29–31). The convergence of inflammatory, metabolic, and redox pathways observed here supports a model in which ferroptosis acts as a mechanistic intermediary linking chronic metabolic stress to progressive tissue injury(29, 32, 33).

From a translational perspective, these findings have several important implications. First, the identified circulating proteins may serve as accessible biomarkers of ferroptosis-associated stress, enabling early detection of individuals at risk for metabolic and cardiovascular complications (34, 35). Second, the strong association between HbA_{1c} and ferroptotic signatures suggests that improved glycaemic control may mitigate ferroptosis-related damage, providing a mechanistic rationale for tight metabolic regulation (29, 36). Third, therapeutic strategies targeting ferroptosis, such as modulation of iron handling, enhancement of antioxidant defenses (e.g., GPX4 activity), or inhibition of lipid peroxidation, may represent promising avenues for intervention in obesity and T2DM (37, 38). In a mouse model of combined obesity and hypertension-induced heart failure with preserved ejection fraction, ferroptosis was decreased by treatment with levosimendan, as evidenced by an up-regulation of GPX4 (39). While such approaches remain largely experimental, our data provide human-based support for their potential relevance.

Several limitations of this study should be considered. The cross-sectional design precludes causal inference, and the observed associations cannot establish whether ferroptosis is a driver or consequence of metabolic dysfunction. The proteomic panel, while comprehensive for inflammatory pathways, does not directly measure key lipid peroxidation products or iron-related metabolites, which would strengthen mechanistic interpretation (40, 41). Additionally, although the cohort is well-characterized, external validation in independent populations is required to confirm generalizability. Insulin resistance was estimated by HOMA-IR rather than directly measured using clamp-based methods. Finally, residual confounding from unmeasured variables, including diet, medication use, or physical activity, cannot be excluded.

Future studies should integrate multi-omic approaches(39, 42) including lipidomics and metabolomics, to directly quantify ferroptosis-related intermediates, such as oxidized phospholipids and labile iron pools. Longitudinal analyses will be essential to determine whether ferroptosis-associated signatures predict disease progression or response to intervention. Experimental studies linking circulating proteomic changes to tissue-specific ferroptotic activity will further clarify causality and therapeutic potential.

Conclusions

This study provides human evidence that metabolic dysfunction is associated with systemic activation of ferroptosis-related molecular pathways. Using plasma proteomics in a well-characterized cohort, we identified a coordinated signature of redox-responsive proteins linking inflammation, iron homeostasis, and lipid peroxidation across the obesity–type T2DM continuum. Importantly, glycaemic dysregulation, rather than adiposity alone, emerged as the primary determinant of ferroptosis-associated proteomic alterations. Individuals with higher HbA_{1c} and T2DM exhibited a pronounced shift toward a pro-ferroptotic state, characterized by increased expression of oxidative stress–related proteins (including IL-6, CXCL9, CCL11, CDCP1, and FGF-21) and reduced anti-inflammatory and regulatory mediators such as IL-10RB and LAP–TGF- β 1. These findings support a model in which ferroptosis acts as a mechanistic intermediary linking chronic metabolic stress to tissue damage in obesity and diabetes. Circulating proteomic signatures may provide clinically accessible markers of ferroptosis-associated stress and offer potential for early risk stratification.

Declarations

Human Ethics and Consent to Participate declarations

Data from the FAT associated Cardiovascular dysfunction (FATCOR) study, which was conducted between 2009-2017 at Haukeland University Hospital, Bergen, Norway. The FATCOR study was performed with approval from the Regional Committees for Medical and Health Research Ethics Western Norway (approval number REK17173) and in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

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AI Disclosure statement

All images included in this work were created using Canva® under human supervision, with manual editing and review to ensure accuracy and consistency. Editing in English was supported by the InstaText® tool, with all suggestions carefully reviewed and approved by the authors.

DATA AVAILABILITY STATEMENT

None.

Disclosure of interest

HH, KM and GK none. EG Boehringer Ingelheim, Amgen, Omron, Menarini Foundation (speaker honorarium), European Society of Cardiology, Council on hypertension nucleus member. HM Boehringer Ingelheim, Bayer, Pfizer (speaker honorarium).

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Figures



Figure 1

Ferroptosis Risk Score across metabolic groups. The ferroptosis risk score (standardized, a.u.) is shown across individuals stratified by metabolic status (lean, obese, and type 2 diabetes mellitus [T2DM]). The score was derived from circulating proteins significantly associated with metabolic traits, integrating pro- and anti-ferroptotic signals. Statistical comparisons were performed using the Kruskal–Wallis test followed by Dunn’s post hoc test with multiple testing correction.

Ferroptosis Score vs HbA1c

Evaluating if Diabetes is a better predictor than BMI

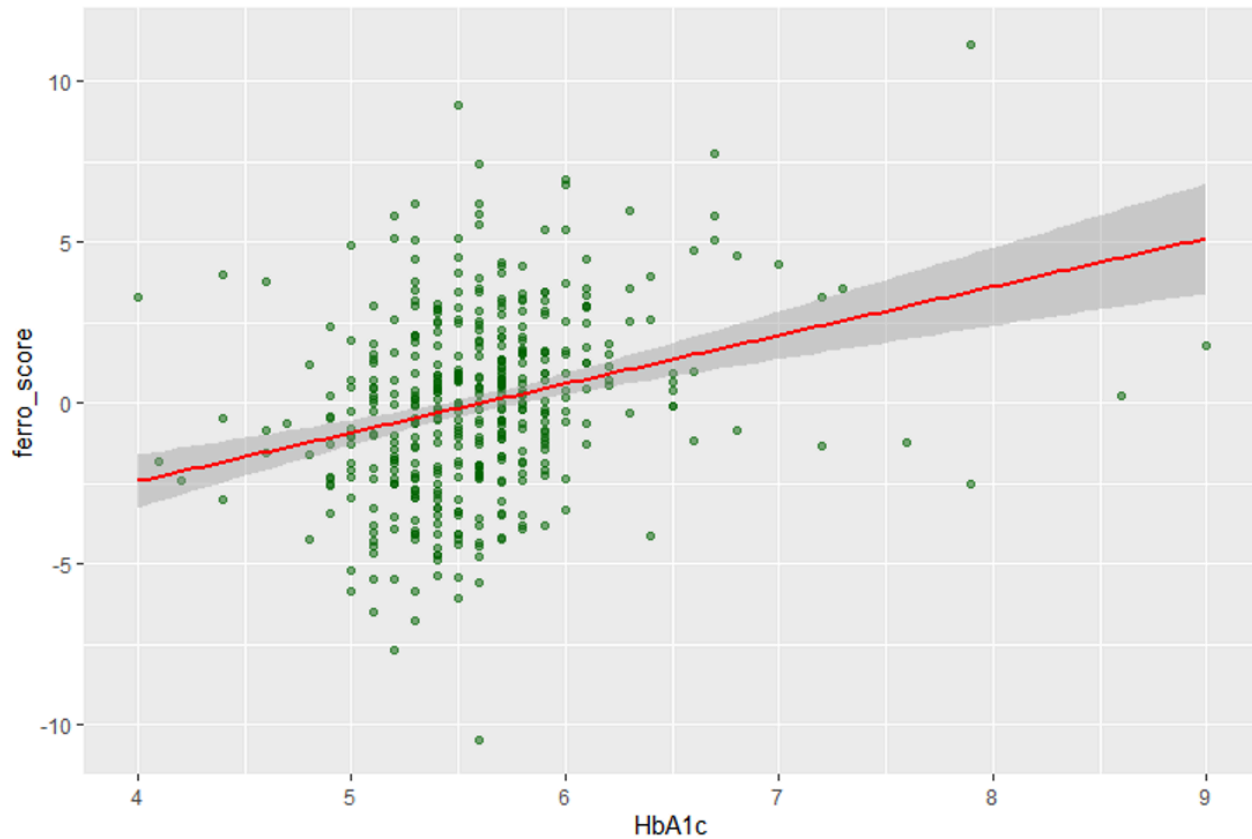


Figure 2

Association between ferroptosis risk score and metabolic parameters.

Scatter plots showing the relationship between the ferroptosis risk score (standardized, a.u.) and (A) body mass index (BMI) and (B) glycated hemoglobin (HbA1c). Associations were assessed using Spearman's rank correlation coefficient (ρ).

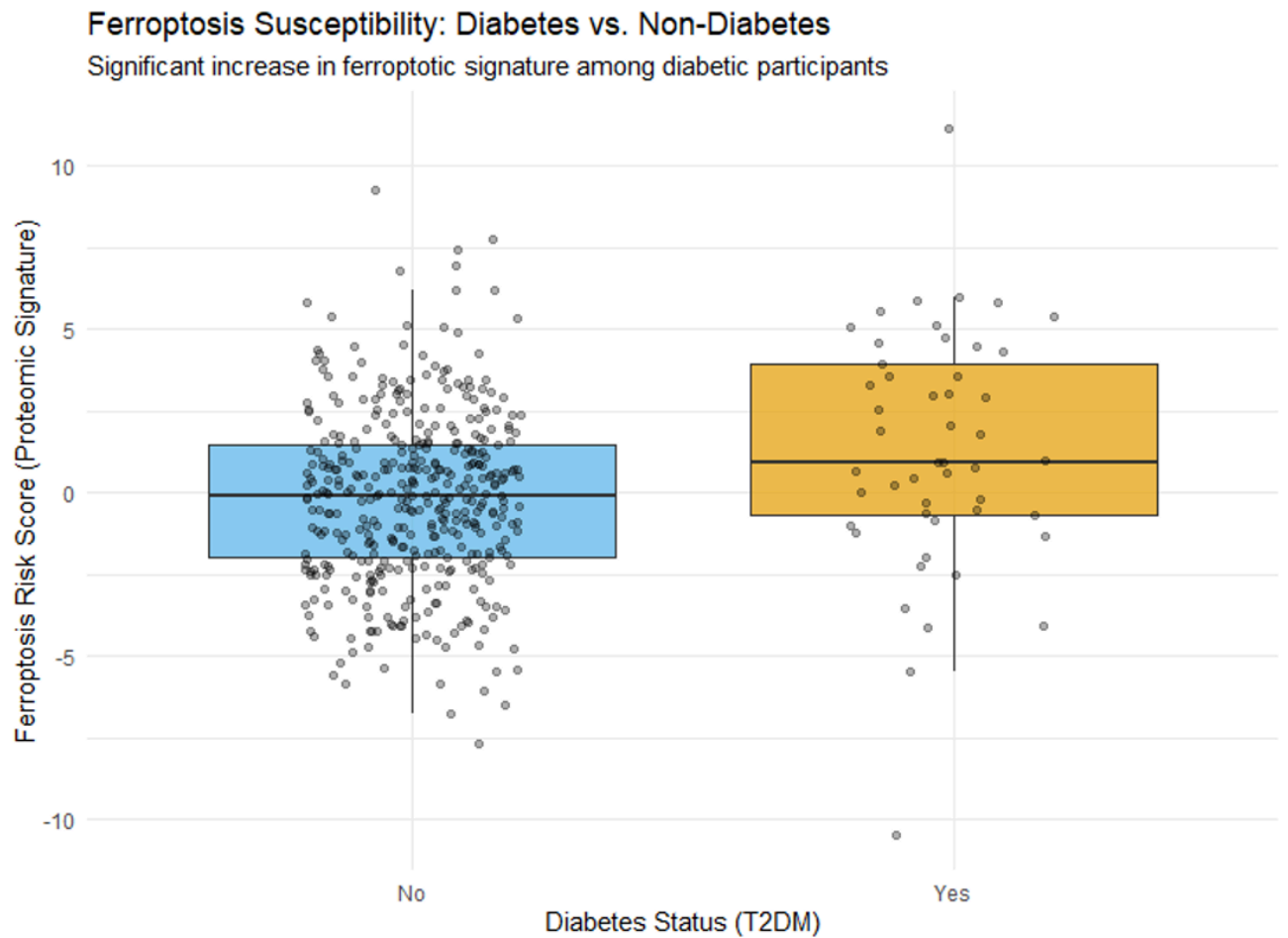


Figure 3

Ferroptosis Risk Score according to T2DM status. Comparison of ferroptosis risk score (standardized, a.u.) between individuals without and with type 2 diabetes mellitus (T2DM). Differences between groups were assessed using the Mann–Whitney U test.

Glycaemic Load & Ferroptotic Priming

Relationship between HbA1c levels and proteomic susceptibility

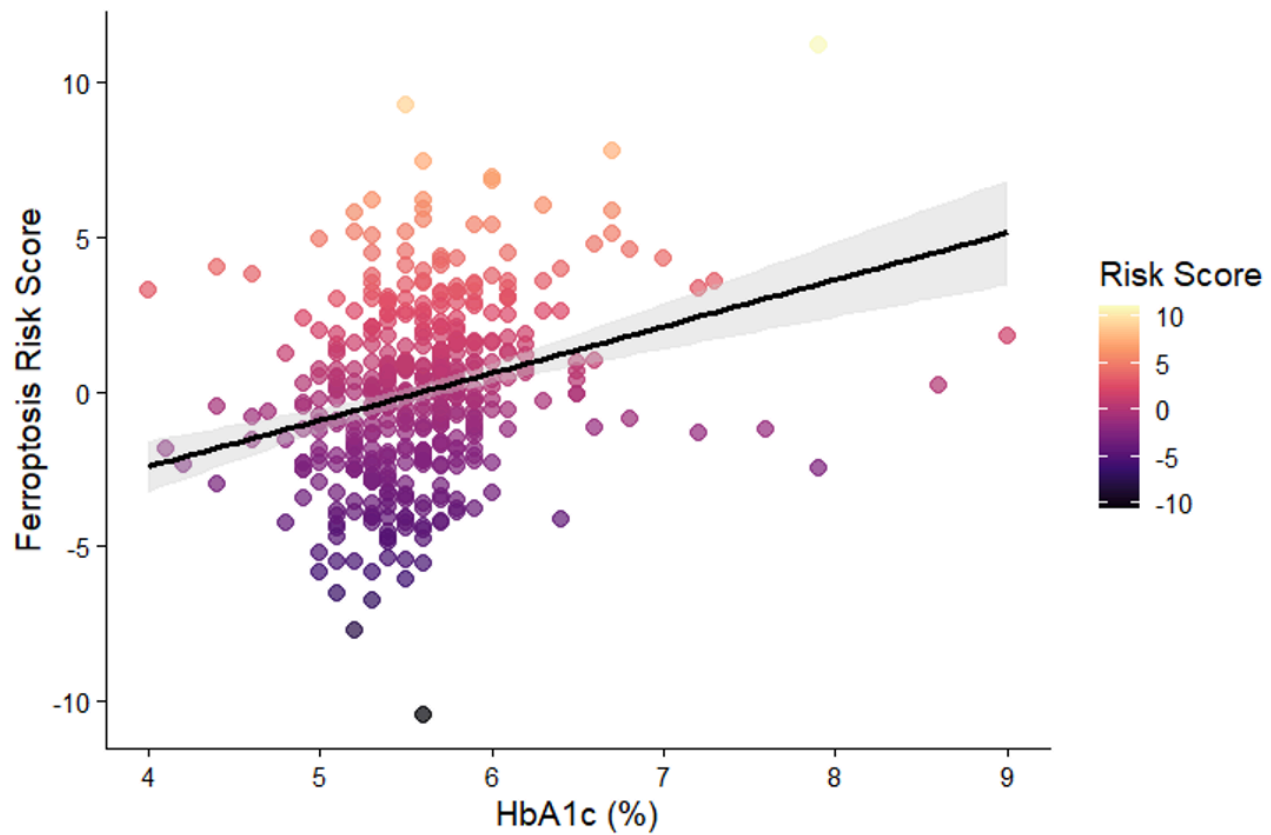


Figure 4

Protein components contributing to the ferroptosis risk score.

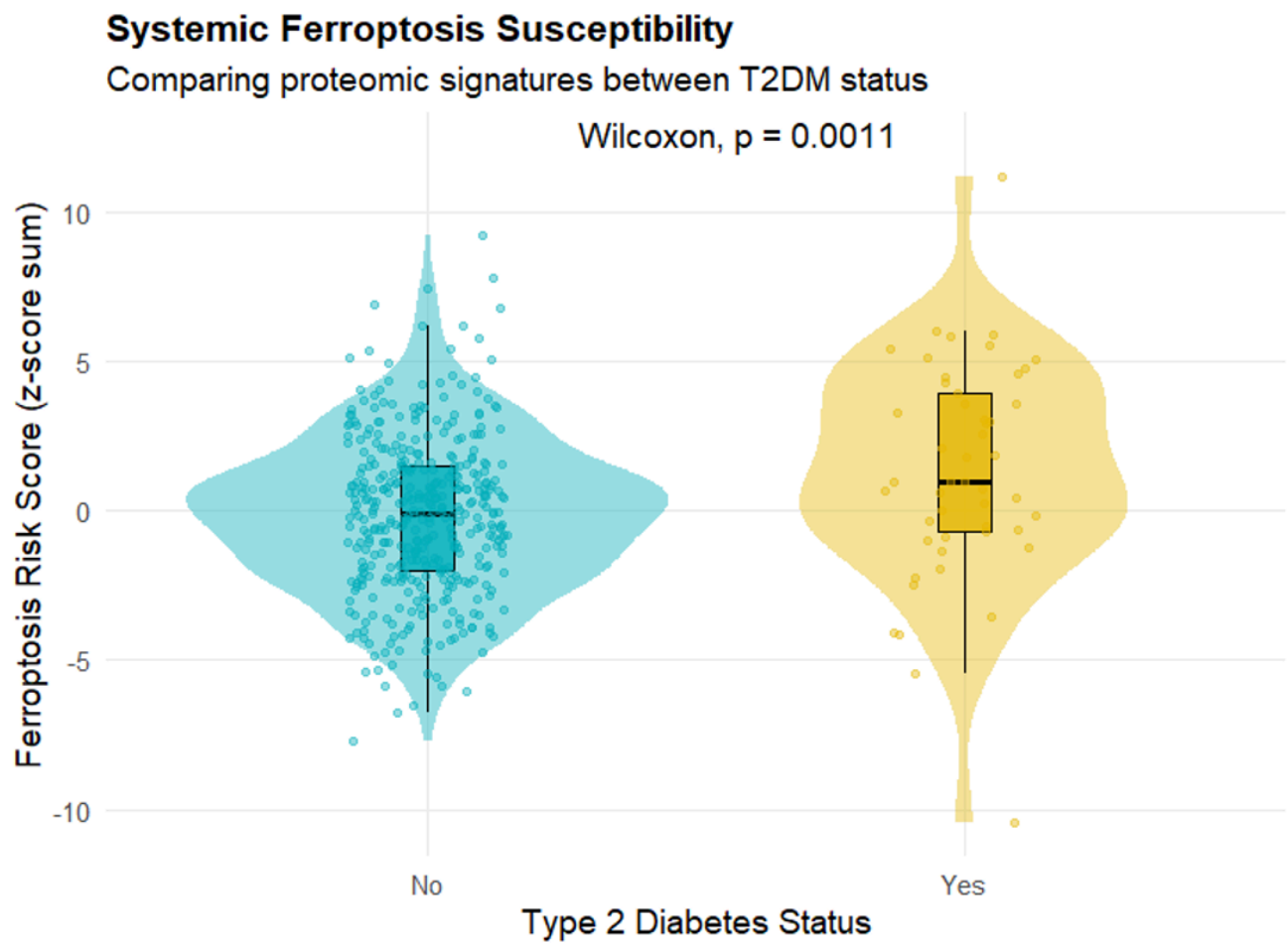


Figure 5

Glycaemic load and ferroptosis risk score.

Supplementary Files

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