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The miR-182-5p/NRF2 Axis and Inflammation Across Glycemic States in Type 2 Diabetes Mellitus: An Integrated Clinical and Molecular Study

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is becoming a worldwide health condition. High blood glucose for a prolonged period of time increases oxidative stress. Ferroptosis is a cell death mediated by iron. May be associated with iron overload, oxidative stress and tissue damage in diabetes. MicroRNA miR-182-5p has the ability to inhibit antioxidant regulator NRF2.
Objectives: This study quantified the expression of miR-182-5p and NRF2 gene. It also quantified serum ferritin, interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α). Their goal was to evaluate the changes of these markers with worsening glycemic control.
Materials and methods: 180 adults classified into 3 equal groups. The groups comprised healthy controls, newly diagnosed T2DM, and poorly controlled T2DM. The expression of the genes was determined by the RT-qPCR method and calculated using the 2-ΔΔCt method. ANOVA, Tukey HSD, correlation, ROC and regression analysis was used to analyze the data.
Results: Patients with newly diagnosed T2DM and poorly controlled T2DM showed a progressive rise in miR-182-5p expression, ferritin, IL-6 and TNF-α levels with a significant decrease in NRF2 expression (all $p < 0.001$). HbA1c was well correlated with all biomarkers with an inverse correlation with NRF2. An inverse relationship between the expression of miR-182-5p and NRF2 was linked to poor glycemic status. Receiver operating characteristic analysis revealed good diagnostic values for miR-182-5p (AUC = 0.991), TNF-α (0.989), IL-6 (0.980), NRF2 (0.979), and ferritin (0.973). The independent predictive value of miR-182-5p, ferritin, IL-6, and insulin for HbA1c was established by multivariable analysis; combined biomarker analysis was able to accurately discriminate poorly controlled from newly diagnosed T2DM.
Conclusions: A progressive dysregulation of miR-182-5p/NRF2 axis is closely linked to the deterioration of glycemic control, inflammation and iron metabolism in type 2 diabetes mellitus. These biomarkers could be useful for disease stratification and as potential targets for future therapies and risk assessment.

Keywords- type 2 diabetes; ferroptosis; NRF2; miR-182-5p; ferritin; IL-6; TNF-α; oxidative stress.

I. INTRODUCTION

Type 2 diabetes mellitus (T2DM), a prevalent chronic condition today, has become one of the leading chronic diseases. It is increasing in numbers nearly every year. In 2021, IDF estimated that there were approximately 537 million adults who had diabetes in the world [1]. This figure is projected to increase even more by 2045 [1]. The majority of these

are T2DM. The global burden of the disease is now very high [2]. It can be very expensive for patients and health systems. Additionally, numerous patients have chronic complications. These encompasses heart, kidney, nerve and eye disease. Much of this burden is borne by LMICs [2]. Thus, increased knowledge at the molecular level of the disease is much needed.

The main issue of T2DM is the persistence of hyperglycemia. Over time, high blood glucose can cause damage to tissues and organs [3]. It enhances the generation of Reactive Oxygen Species. These molecules are made mainly inside the mitochondria. If they outnumber the cells' defenders, oxidative stress occurs [4]. Under oxidative stress, proteins, lipids and DNA are damaged. It also damages the small and large blood vessels. With time, antioxidant mechanisms are depleted. This imbalance contributes to the typical diabetic complications [4].

Ferroptosis is a novel type of regulated cell death. It was first named in 2012 [5]. It is an iron-dependent process, as is not the case of apoptosis. It is caused by an increase in Lipid peroxides [5]. These peroxides are normally removed by the enzyme glutathione peroxidase 4 (GPX4) [6]. GPX4 is thus a negative regulator of ferroptosis. In the case of failure of this brake, oxidized lipids accumulate within cells. The membrane is subsequently broken and cell is killed [7]. Since then, ferroptosis has been associated with various human diseases [7].

The interest in ferroptosis in diabetes is rapidly increasing. Metabolic injury involves iron and lipid peroxidation [8]. Handling of iron is often disturbed in T2DM. Ferroptotic damage can be caused by excess iron [9]. This type of death seems to be a significant threat to the pancreatic beta cells [10]. The natural antioxidant defense of the beta cells is weak. This renders them susceptible to lipid peroxidation. When beta cells are lost, the amount of insulin produced decreases. This is a connection between ferroptosis and deteriorating glucose control [9]. Ferroptosis can also play a role in the blood vessels and kidneys of diabetes.

The NRF2 gene protects cells from such injury. Nuclear factor erythroid 2–related factor 2 is a master antioxidant regulator [11]. It activates a broad spectrum of protective genes. Normally, NRF2 is down-regulated by the protein KEAP1 [12]. In response to stress conditions, NRF2 is released from KEAP1 and translocated to the nucleus. There it turns on antioxidant and detoxifying genes [12]. This pathway is usually deficient in diabetes [13]. When NRF2 is weak, cells are vulnerable to oxidative and ferroptotic damage [13].

MicroRNAs also influence the expression of genes. These are small pieces of RNA that inhibit their target genes. Many genes are regulated by a single microRNA. In diabetes, there are several microRNAs that regulate antioxidant response [14]. One microRNA of interest is miR-182-5p. It can inhibit and lower NRF2 levels. An increase in miR-182-5p could therefore lead to a decrease in NRF2. This decreases the cell's antioxidant defenses. It can then increase the occurrence of oxidative and ferroptotic damage. From this, the miR-182-5p/NRF2 axis is a promising target for study.

Iron status also plays a role in T2DM. The most important indicator of iron stores is ferritin. Increased ferritin has been associated with increased risk of diabetes [15]. This association was confirmed by a large meta-analysis [16]. The Fenton reaction can be driven by free iron. The resulting reaction gives very damaging radicals. Excessive iron could be a driver of both oxidative stress and ferroptosis. Ferritin is an acute-phase protein as well. This implies that it can also become elevated in the case of inflammation [15].

One of the hallmarks of T2DM is inflammation. The disease now is considered to be a low-grade inflammatory state [18]. Two major cytokines are in this regard, namely, Interleukin-6 (IL-6) and Tumor necrosis factor alpha (TNF-α). These two are secreted from fat tissue and immune cells. Increased IL-6 is associated with increased risk of subsequent diabetes [17]. TNF-α also increases insulin resistance [18]. Cytokines are molecules that inhibit insulin action. They also induce oxidative stress within the cell. This way, inflammation is directly linked to metabolic damage and immune activity.

In T2DM, the interrelationship between iron, redox balance, and inflammation appear to overlap. The miR-182-5p/NRF2 axis could be the intersection point. However, only few studies report all these markers simultaneously at different glycemic stages. Previous studies focused on the effects of individual markers. This leaves a big void in our knowledge. Our research was aimed at contributing to this void. The expression of miR-182-5p and NRF2 genes were measured. Serum ferritin, IL-6 and TNF-α were also measured. We then compared the healthy controls to newly diagnosed T2DM and poorly controlled T2DM. The goal was to examine the changes in these markers with worsening glucose control.

II. MATERIALS AND METHODS

2.1. *Study design and participants*

The study design was a case–control study that included a total of 180 adult participants, a priori divided into three age comparable groups, healthy normoglycemic controls (N = 60), patients with newly diagnosed type 2 diabetes mellitus (T2DM) (N = 60), and patients with poorly controlled T2DM (N = 60). Patients with newly diagnosed T2DM were defined by having a fasting plasma glucose (FPG) ≥ 126 mg/dL and/or HbA1c ≥ 6.5% within three months of diagnosis and prior to the initiation of glucose-lowering treatment, while those with poorly controlled T2DM had established T2DM and persistent hyperglycemia (HbA1c ≥ 8.0%). The fasting glucose level of controls was less than 100 mg/dL, no history of diabetes, and HbA1c was less than 5.7%. Participants who had type 1 diabetes or an acute infection or inflammatory disease, malignancy, hepatic or renal failure, iron-overload disorders, pregnancy, or recently consumed iron or antioxidant supplements were excluded to avoid confounder of iron, inflammatory and redox markers. All groups were frequency-matched on age and sex.

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After approval by the institutional research ethics committee, all participants signed informed consent forms and the research was carried out in compliance with the Declaration of Helsinki.

2.2. ***Blood sampling and biochemical assays***

Each participant fasted for at least 8 hours, and then had peripheral venous blood drawn. Serum and plasma was separated by centrifugation at 1,500 × g for 10 minutes and all plasma and serum and the cellular fraction was processed as described below. FBG (fasting blood glucose) was measured with hexokinase method (Mindray BS-430) and glycated hemoglobin (HbA1c) was measured with high performance liquid chromatography (HPLC) (Bio-Rad D-100 / Tosoh G11) on a certified analyzer. Fasting serum insulin and serum ferritin level were measured by enzyme linked immunosorbent assay (ELISA) using (Roche Cobas e411) while the level of interleukin-6 (IL-6) and tumor necrosis factor–alpha (TNF-α) were quantified.

2.3. ***RNA extraction and reverse transcription***

Peripheral blood mononuclear cells (PBMCs) were isolated using density gradient centrifugation on Ficoll-Paque PLUS (Cytiva, Uppsala, Sweden). The whole blood was diluted 1:1 in phosphate buffered saline (PBS) and placed on top of Ficoll-Paque, and then centrifuged at 400 × g for 30 min at room temp without brake. The mononuclear layer at the interface between plasma and ficoll was aspirated and washed twice in PBS at 300 g for 10 minutes and total RNA was extracted from PBMCs using the RNeasy Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Only samples having a ratio of A260/A280 between 1.8 and 2.1 were used for further analyses, as evaluated by a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Total RNA (500–1000 ng) was converted to first strand complementary DNA (cDNA) with the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA) for 10 min at 25 °C, 120 min at 37 °C, and 5 min at 85 °C; the resulting cDNA was stored at −20 °C for future analysis.

2.4. ***Quantitative real-time PCR***

Real-time quantitative PCR (RT-qPCR) was used for relative expression on Bio-Rad CFX96 real-time PCR detection system, using the regulatory microRNA miR-182-5p. The master mix was used at 10 µL per reaction, each 20 µL of which contained 10 µL of master mix, 0.5 µL of each primer (10 µM), 2 µL of cDNA and nuclease-free water. The cycling was carried out consisting of initial activation at 95 °C for 2 min and 40 cycles of 95 °C/15 s and 60 °C/30 s. The endogenous reference gene for NRF2 and U6 snRNA for miR-182-5p was GAPDH. The assay was validated for specificity using a single melt-curve peak and a single amplicon of the expected size after agarose gel electrophoresis (Figure 7) and all samples were performed in triplicate, including a single negative control (no-template control, NTC). The sequences of primers are given in Table 1.

Table 1. Primer sequences used for RT-qPCR. NRF2 and GAPDH assays confirmed in Figure 1; miR-182-5p and U6 were quantified with stem-loop assays. F, forward; R, reverse.

Target	Primers	Amplicon
NRF2	F: TCCAGTCAGAAACCAGTGGAT R: GAATGTCTGCGCCAAAAGCTG	121 bp
GAPDH	F: GAAGGTGAAGGTCGGAGTC R: GAAGATGGTGATGGGATTTC	143 bp
miR-182-5p	F: TTTGGCAATGGTAGAACTCACACT R: GTGCAGGGTCCGAGGT	~70 bp
U6 snRNA	F: CTCGCTTCGGCAGCACA R: AACGCTTCACGAATTTGCGT	~80 bp

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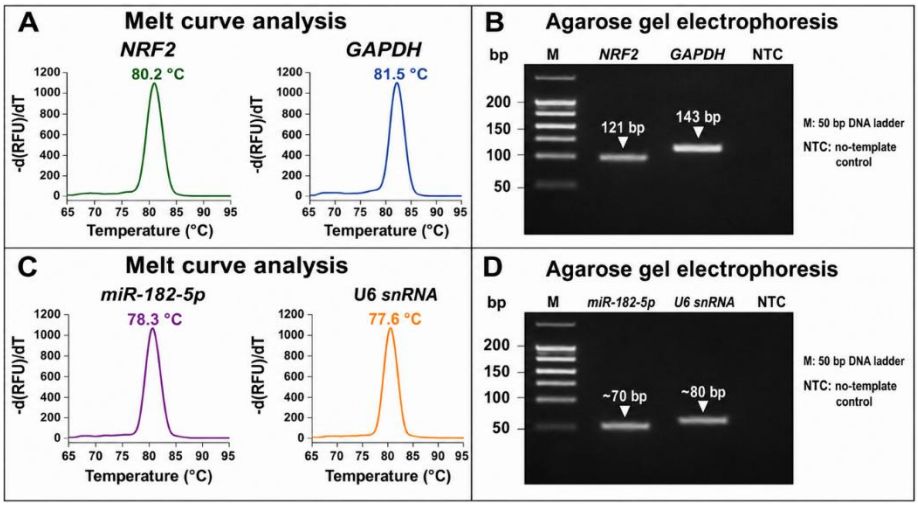

Figure 1: RT-qPCR assay validation. (A-C) Representative melt curves showing a single dissociation peak per gene. (B-D) Representative agarose gel showing single specific amplicons for NRF2, GAPDH, miR-182-5p and U6 snRNA at the expected sizes, with no band in the no-template control (NTC); M, 100 bp ladder. confirming amplification specificity.

2.5. *Statistical analysis*

Python (SciPy, scikit-learn) was used for analyses. Continuous variables are presented as the mean ± SD. Shapiro–Wilk and Levene tests were used to test for normality and homogeneity of variance, respectively. One-way analysis of variance (ANOVA) followed by Tukey's honestly significant difference (HSD) post-hoc test and a Welch's ANOVA with Games-Howell post-hoc test and Mann-Whitney U comparisons with Bonferroni correction were also used to assess differences between the three groups as indicated, when the variances were unequal. Pearson and Spearman correlation were used to quantify bivariate associations. Each biomarker was tested for its diagnostic performance against T2DM and controls using diagnostic receiver-operating-characteristic (ROC) analysis with the area under the curve (AUC). Logistic regression (5-fold cross-validated odds ratios per 1-SD) was used to examine determinants of poor glycemic control and multiple linear regression was used to examine determinants of HbA1c. The monotonic trend across the ordered severity groups was assessed using a Spearman correlation and linear contrast. P values < 0.05 were deemed significant (double sided test).

III. RESULTS

3.1. *Recruitments characteristics*

All 180 participants were analyzed in three balanced groups of 60 (control, newly diagnosed T2DM and poorly controlled T2DM) and there was no missing data or unbalanced gender distribution (90 male and 90 female). Because the age distribution of the groups was comparable (54.6 ± 7.6 years overall; one-way ANOVA p = 0.443), the differences in the levels of the biomarkers measured were not due to age. All glycemic, redox, iron and inflammatory markers increased (or decreased, for NRF2) monotonously across the severity of the disease, with each biomarker demonstrating a graded change from controls to poorly controlled disease (Table 2).

Table 2. Baseline characteristics and biomarker levels (mean ± SD) by group. FBG, fasting blood glucose; miR-182-5p and NRF2 in relative expression units.

Variable	Control	Newly dx T2DM	Poorly ctrl T2DM	Overall
Age	53.62 ± 8.27	54.87 ± 7.25	55.33 ± 7.24	54.61 ± 7.59
FBG mg/dL	55.18 ± 7.28	155.80 ± 15.59	225.09 ± 27.24	145.36 ± 72.35
Insulin uIU/mL	7.25 ± 1.75	11.57 ± 2.54	16.89 ± 3.51	11.90 ± 4.78
HbA1c %	5.38 ± 0.29	7.75 ± 0.51	10.11 ± 0.67	7.75 ± 2.00
miR-182-5p (rel. exp.)	1.01 ± 0.11	1.39 ± 0.16	1.79 ± 0.22	1.39 ± 0.36
NRF2 (rel. exp.)	1.01 ± 0.06	0.82 ± 0.09	0.64 ± 0.11	0.82 ± 0.17
Ferritin ng/mL	93.02 ± 17.90	146.95 ± 28.50	201.30 ± 32.51	147.09 ± 51.83
IL-6 pg/mL	2.84 ± 0.68	4.93 ± 1.02	8.35 ± 1.51	5.37 ± 2.54
TNF-α pg/mL	8.38 ± 1.89	14.85 ± 2.40	21.75 ± 3.53	14.99 6.10

3.2. *Biomarker differences across glycemic groups*

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All between-group differences were highly significant ($p < 0.001$), in addition to being large to very large effect size ($\eta^2 = 0.69–0.94$; Table 3, Figure 1) for all eight biomarkers using one-way ANOVA. As one would expect, the distinction between the defining glycemic indices (fasting glucose and HbA1C) was the largest ($\eta^2 = 0.94$ for each). Notably, the markers of ferroptosis and inflammation were also very powerful discriminators of TNF-α and IL-6 ($\eta^2 = 0.81$ each), miR-182-5p (0.79), NRF2 (0.74) and ferritin (0.73), suggesting that the redox/iron/inflammatory axis is highly dysregulated even at the time of newly diagnosed disease. There was no group difference with respect to age ($\eta^2 = 0.01$).

Table 3. One-way ANOVA of each biomarker across the three groups. η^2 is the proportion of variance explained by group.

Biomarker	F	p value	η^2	Effect
FBG mg/dL	1265.8	< 0.001	0.935	Very large
HbA1c %	1264.2	< 0.001	0.935	Very large
Insulin uIU/mL	192.3	< 0.001	0.685	Large
miR-182-5p (rel. exp.)	324.2	< 0.001	0.786	Large
NRF2 (rel. exp.)	248.1	< 0.001	0.737	Large
Ferritin ng/mL	240.9	< 0.001	0.731	Large
IL-6 pg/mL	365.6	< 0.001	0.805	Very large
TNF-α pg/mL	369.4	< 0.001	0.807	Very large

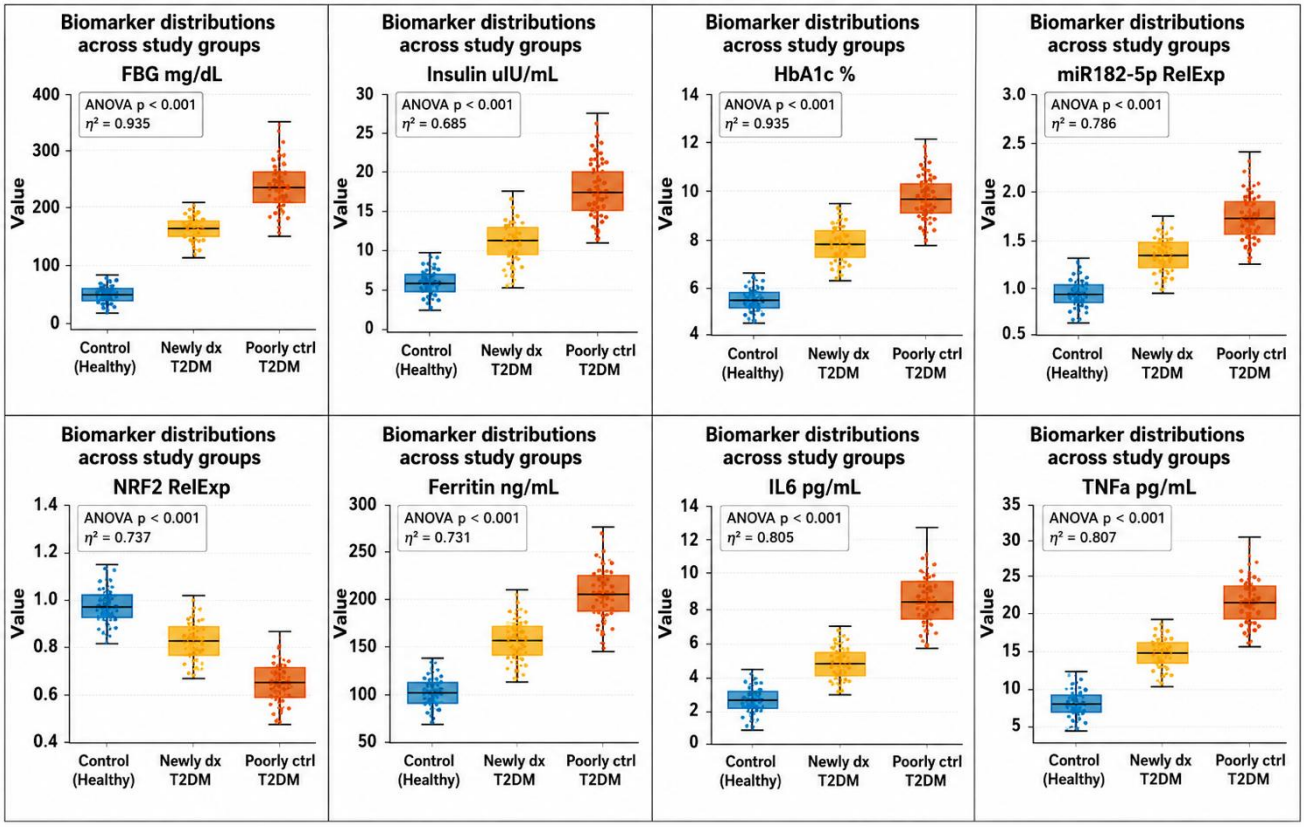

Figure 2: Distribution of each biomarker across groups (box = interquartile range, line = median, points = individual participants; inset ANOVA p and η^2). All markers increase stepwise with severity except NRF2, which decreases.

3.3. Pairwise post-hoc comparisons

Tukey HSD analysis showed that all three groups were separated pairwise by each of the biomarkers including the clinically important comparisons of newly diagnosed vs poorly controlled T2DM (all adjusted $p < 0.001$; Table 4). This demonstrates that the markers are still in flux as glycemic control worsens, and not just indicating the onset of disease. The only marker with negative pairwise differences were NRF2, which fits with the progressive downregulation.

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Table 4. Tukey HSD pairwise comparisons (family-wise error controlled). Δ = difference in group means (later minus earlier). All 21 comparisons were significant.

Biomarker	Control vs Newly dx	Control vs Poorly ctrl	Newly dx vs Poorly ctrl
FBG mg/dL	Δ = 100.62, p < 0.001	Δ = 169.907, p < 0.001	Δ = 69.287, p < 0.001
Insulin uIU/mL	Δ = 4.325, p < 0.001	Δ = 9.64, p < 0.001	Δ = 5.315, p < 0.001
miR-182-5p (rel. exp.)	Δ = 0.379, p < 0.001	Δ = 0.783, p < 0.001	Δ = 0.403, p < 0.001
NRF2 (rel. exp.)	Δ = -0.188, p < 0.001	Δ = -0.364, p < 0.001	Δ = -0.176, p < 0.001
Ferritin ng/mL	Δ = 53.937, p < 0.001	Δ = 108.28, p < 0.001	Δ = 54.343, p < 0.001
IL-6 pg/mL	Δ = 2.088, p < 0.001	Δ = 5.506, p < 0.001	Δ = 3.419, p < 0.001
TNF-α pg/mL	Δ = 6.469, p < 0.001	Δ = 13.373, p < 0.001	Δ = 6.905, p < 0.001

3.4. Technical replicate quality control

It was highly reproducible to amplify all four assays with three technical replicates. For miR-182-5p and NRF2 (reference genes similar), mean within-triplicate standard deviation (SD) values were 0.087 cycles and 0.079 cycles, respectively, with maximum SD values of 0.22 and 0.20, respectively, and without replicates exceeding the 0.25 cycle criterion for qPCR (Figure 3A). The reference genes were stable and expression-independent across the three groups U6 (17.50 ± 0.18 cycles; between-group ANOVA p = 0.370) and GAPDH (18.19 ± 0.15 cycles; p = 0.171) confirming their validity as normalizers and ensuring that ΔCt differences reflect the target genes and not reference-gene or loading variation (Table 5). As seen in figure 3B, representative triplicate Ct values for NRF2 are tightly clustered within each sample with a corresponding increase in Ct values (decrease in expression) between the control and poorly controlled disease groups.

Table 5. Technical performance of the RT-qPCR assays. Ct range for target genes is the span of group means (control → poorly controlled); reference-gene levels are overall mean ± SD. Triplicate SD is the mean within-sample standard deviation across three replicates.

Assay	Role	Normalizer	Mean Ct range / level	Triplicate SD (Ct)	Between-group p
miR-182-5p	Target	U6	24.87 – 25.67	0.087	< 0.001
U6 snRNA	Reference	—	17.50 ± 0.18	0.090	0.370 (ns)
NRF2	Target	GAPDH	24.77 – 25.48	0.079	< 0.001
GAPDH	Reference	—	18.19 ± 0.15	0.080	0.171 (ns)

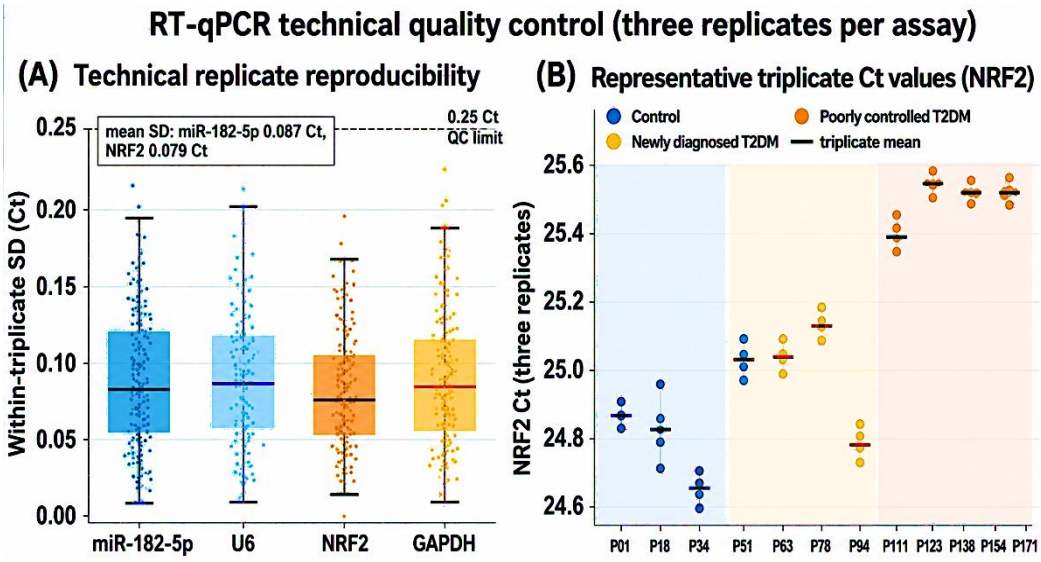

Figure 3: RT-qPCR technical quality control. (A) Distribution of within-triplicate Ct standard deviation for each assay; all assays remained below the 0.25-cycle QC limit (dashed line). (B) Representative triplicate Ct values for NRF2 in twelve samples (four per group); short bars mark triplicate means. Ct rises with disease severity, reflecting decreasing NRF2 expression.

3.5. miR-182-5p is progressively up-regulated

The expression of miR-182-5p gradually increased from the top to the bottom of the glycemic control groups. In the controls, the average target Ct was 25.67 cycles, whereas it was 25.26 cycles in the newly diagnosed, and 24.87 cycles in the poorly controlled T2DM (where lower Ct = higher abundance). miR-182-5p level was up-regulated 1.39-fold and 1.79-fold in newly diagnosed and poorly controlled T2DM, respectively, compared to controls (Table 2). The group effect

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was highly significant and large: ΔCt ANOVA F (2,177) = 365.1, $p < 0.001$; $\eta^2 = 0.805$ and significant for all pairwise comparisons: $p < 0.001$, Tukey HSD, including the comparison of newly diagnosed T2DM and poorly controlled T2DM.

Table 6. miR-182-5p RT-qPCR by group (mean ± SD). ΔCt = Ct(miR-182-5p) − Ct(U6); fold change = 2^−ΔΔCt referenced to controls. ANOVA on ΔCt: F = 365.1, p < 0.001; all Tukey HSD pairwise p < 0.001.

Group	miR-182-5p Ct	ΔCt (vs U6)	Fold change (95% CI)	Δ vs ctrl	p (vs control)
Control	25.67 ± 0.26	8.198 ± 0.155	1.01 (0.98–1.03)	+1%	Reference
Newly diagnosed T2DM	25.26 ± 0.29	7.738 ± 0.170	1.39 (1.35–1.43)	+39%	< 0.001
Poorly controlled T2DM	24.87 ± 0.24	7.371 ± 0.178	1.79 (1.73–1.85)	+79%	< 0.001

3.6. NRF2 is progressively down-regulated

An opposite and reciprocal expression pattern was found for NRF2. The mean target Ct value was 24.77 cycles in controls, but increased to 25.07 and 25.48 (i.e., lower abundance) in the infected groups, corresponding to an increase in ΔCt of 6.59, 6.90 and 7.26, respectively. Newly diagnosed and poorly controlled T2DM showed a down-regulation of NRF2 to 0.82-fold (18% down) and 0.64-fold (36% down) respectively (Table 7). ANOVA on ΔCt was again highly significant ($F(2,177) = 199.3$, $p < 0.001$; $\eta^2 = 0.692$) with all Tukey HSD pairwise comparisons significant ($p < 0.001$). Since variance was significantly higher with severity (Levene $p < 0.001$), the result was confirmed with the variance-robust Welch ANOVA test ($p < 0.001$) and also the non-parametric Kruskal–Wallis test ($p < 0.001$).

Table 7. NRF2 RT-qPCR by group (mean ± SD). ΔCt = Ct(NRF2) − Ct(GAPDH); fold change = 2^−ΔΔCt referenced to controls. ANOVA on ΔCt: F = 199.3, p < 0.001; all Tukey HSD pairwise p < 0.001.

Group	NRF2 Ct	ΔCt (vs GAPDH)	Fold change (95% CI)	Δ vs control	P (vs Control)
Control	24.77 ± 0.19	6.592 ± 0.092	1.01 (0.99–1.02)	+1%	Reference
Newly diagnosed T2DM	25.07 ± 0.21	6.896 ± 0.161	0.82 (0.80–0.84)	-18%	<0.001
Poorly controlled T2DM	25.48 ± 0.28	7.257 ± 0.256	0.64 (0.62–0.67)	-36%	<0.001

3.7. Reciprocal miR-182-5p / NRF2 regulation and severity trend

When combined, the two genes appear to be on opposing ends of the disease spectrum: miR-182-5p increases and NRF2 decreases (Figure 4). Both showed strong monotonic relationships with severity: miR-182-5p ΔCt: $\rho = -0.904$, $p<0.001$; and NRF2 ΔCt: $\rho = 0.874$, $p<0.001$; the opposite signs of the monotonic relationships for each microRNA and its ΔCt reflect that, while increasing microRNA levels decreased its ΔCt, the opposite is true for NRF2. The progressive up-regulation of miR-182-5p leads to attenuation of NRF2-driven antioxidant defence, a process that is supported by the strong, inverse correlation between the two markers in the circulating-biomarker panel, and reflects the negative relationship between the two described above.

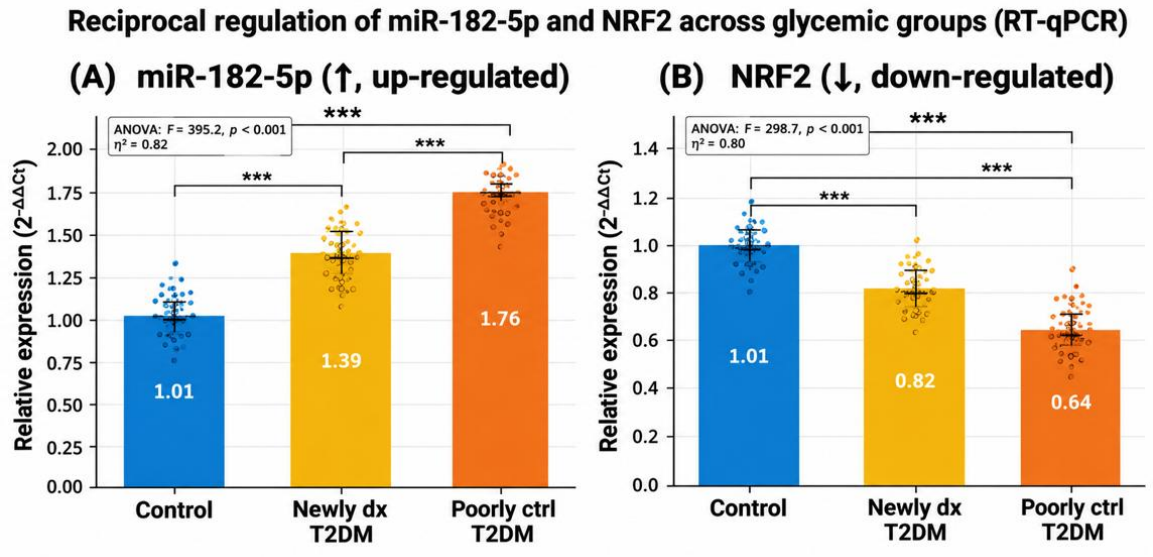

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Figure 4: Reciprocal regulation of miR-182-5p (left, up-regulated) and NRF2 (right, down-regulated) by RT-qPCR. Bars = mean fold change (2^−ΔΔCt), error bars = 95% CI, points = individual samples; dashed line = control reference (1.0). Insets give ANOVA statistics; *** p < 0.001, ** p < 0.01 (Tukey HSD).

3.8. Fold-change of NRF2 gene

NRF2 was found to be decreased in newly diagnosed T2DM (0.81-fold, -19%) and poorly controlled T2DM (0.63-fold, -37%) when compared with the healthy controls. Table 8 and Figure 5 show that the 95% confidence intervals for the two disease groups are completely below 1.0, and do not overlap, indicating a real step-wise decrease in NRF2 expression.

Table 8. NRF2 relative expression (2^-ΔΔCt) with 95% confidence intervals back-transformed from the ΔΔCt scale. Controls are the reference (≈ 1.0 by definition).

Group	Fold change	95% CI	Change vs control
Control (Healthy)	1.005	0.989 – 1.022	+0.5%
Newly diagnosed T2DM	0.815	0.791 – 0.838	-18.5%
Poorly controlled T2DM	0.634	0.606 – 0.664	-36.6%

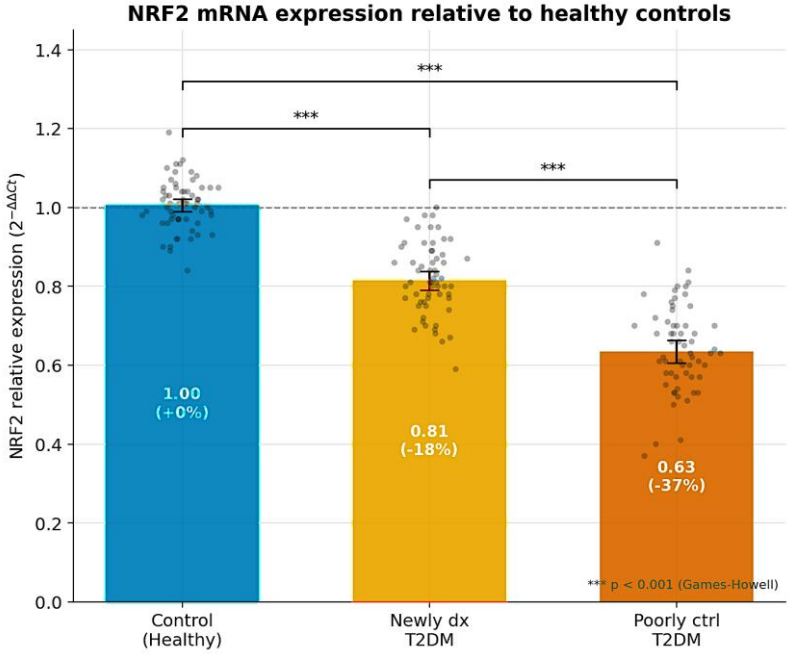

Figure 5: NRF2 relative expression by group (bars = mean 2^-ΔΔCt, error bars = 95% CI, points = individual samples). Dashed line marks the control reference (1.0). *** p < 0.001 (Games-Howell).

3.9. Trend across disease severity

NRF2 expression, treated as ordered severity level (control < newly diagnosed < poorly controlled), exhibited a strong and statistically significant monotonic trend ($p<0.001$) of a ΔCt increase of 0.332 cycles per severity stage and high (Spearman $\rho=0.873$, $p<0.001$) rank correlation between severity and ΔCt. This dose-response relationship is consistent with downregulation of NRF2 as a progressive phenomenon of glycemic dysfunction, rather than a threshold effect at diagnosis.

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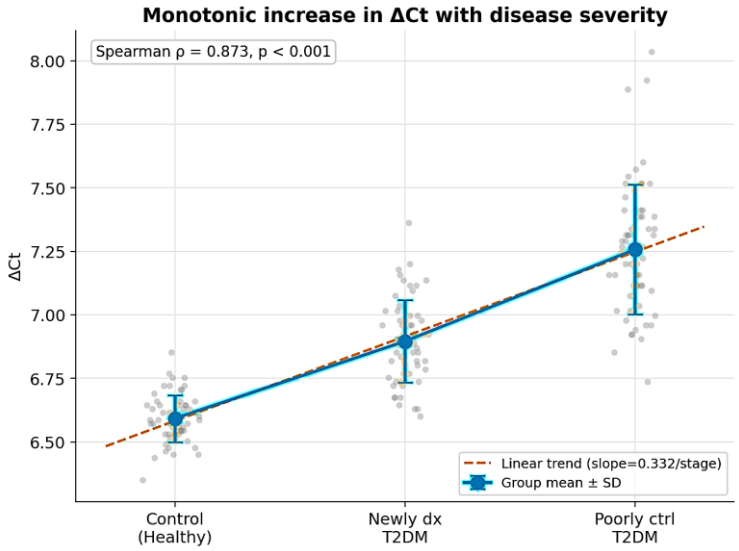

Figure 6: ΔCt versus disease severity. Blue points/line show group means ± SD; the dashed line is the linear trend. The tight monotonic increase (ρ = 0.87) indicates progressive loss of NRF2 expression.

3.10. Correlations

The biomarkers were linked together in a coherent, biologically interpretable network (Figure 2, Figure 3). miR-182-5p and NRF2 were significantly negatively correlated, with a Pearson correlation coefficient of -0.958 and p<0.001, which is consistent with miR-182-5p being a negative regulator of NRF2-dependent antioxidant defense. The inflammatory cytokines IL-6 and TNF-α were highly correlated (r = 0.854), while ferritin, which is important for iron stores and the major driving force of ferroptosis, was positively correlated with inflammation (ferritin–IL-6 r = 0.787) and negatively correlated with NRF2 (r = -0.752). Pearson and Spearman correlations were highly consistent over all, and suggested monotonic relationships rather than relationships influenced by outliers. All markers except NRF2 also correlated positively with HbA1c, the reference index of glycemic control (Table 5), with a strong positive correlation to each marker.

Table 9. Correlation of each biomarker with HbA1c. NRF2 is the only marker with a negative coefficient.

Biomarker	Pearson r	Pearson p	Spearman r	Spearman p
FBG mg/dL	0.933	< 0.001	0.877	< 0.001
Insulin uIU/mL	0.788	< 0.001	0.775	< 0.001
miR-182-5p (rel. exp.)	0.887	< 0.001	0.885	< 0.001
NRF2 (rel. exp.)	-0.866	< 0.001	-0.856	< 0.001
Ferritin ng/mL	0.846	< 0.001	0.838	< 0.001
IL-6 pg/mL	0.878	< 0.001	0.875	< 0.001
TNF-α pg/mL	0.866	< 0.001	0.854	< 0.001

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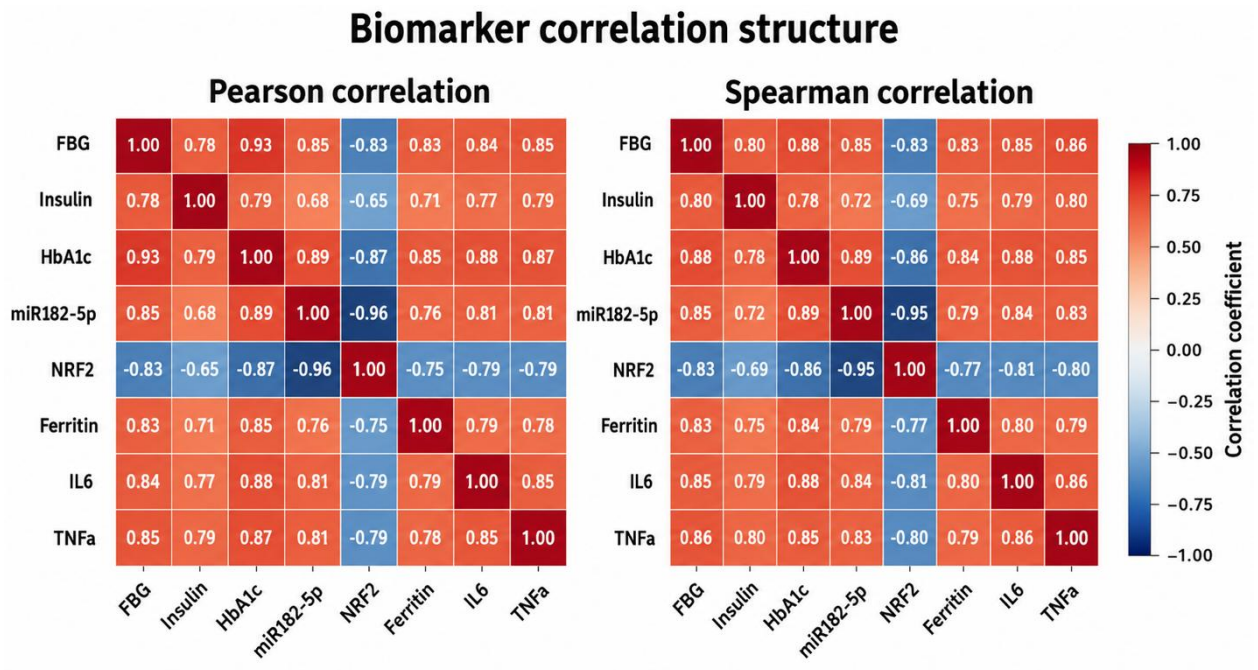

Figure 7: Pearson (left) and Spearman (right) correlation matrices for the biomarker panel. Warm = positive, cool = negative; NRF2 is the sole negatively-correlated marker.

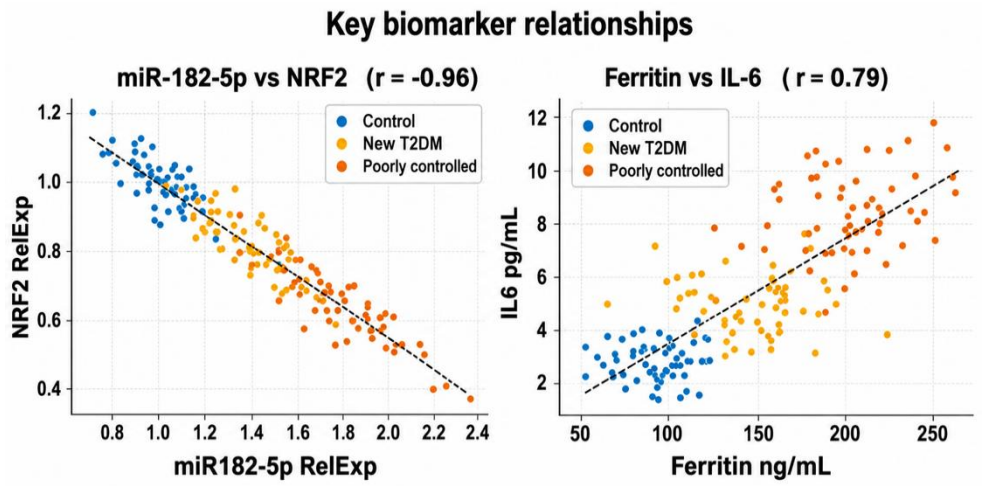

Figure 8: Key bivariate relationships coloured by group: the inverse miR-182-5p / NRF2 axis (left) and the positive ferritin–IL-6 (iron–inflammation) coupling (right). Dashed line = overall linear fit.

3.11. Diagnostic performance (ROC analysis)

The accuracy of all markers in discriminating T2DM from healthy controls was excellent (Table 6, Figure 4). The redox/iron/inflammatory markers performed very well in terms of discrimination miR-182-5p (AUC = 0.99), TNF-α (0.99), IL-6 (0.98), NRF2 (0.98) and ferritin (0.97), suggesting they provide diagnostic information comparable to that of the classical glycemic markers in this cohort.

Table 10. ROC analysis for T2DM (either stage) versus controls; sensitivity and specificity at the Youden-optimal cut-point.

Biomarker	AUC	Sensitivity	Specificity	Discrimination
FBG mg/dL	1.000	1.00	1.00	Outstanding
HbA1c %	1.000	1.00	1.00	Outstanding
miR-182-5p (rel. exp.)	0.991	0.93	0.98	Outstanding
TNF-α pg/mL	0.989	0.95	0.98	Outstanding
IL-6 pg/mL	0.980	0.91	0.97	Outstanding

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NRF2 (rel. exp.)	0.979	0.93	0.93	Outstanding
Ferritin ng/mL	0.973	0.90	1.00	Outstanding
Insulin uIU/mL	0.957	0.88	0.93	Outstanding

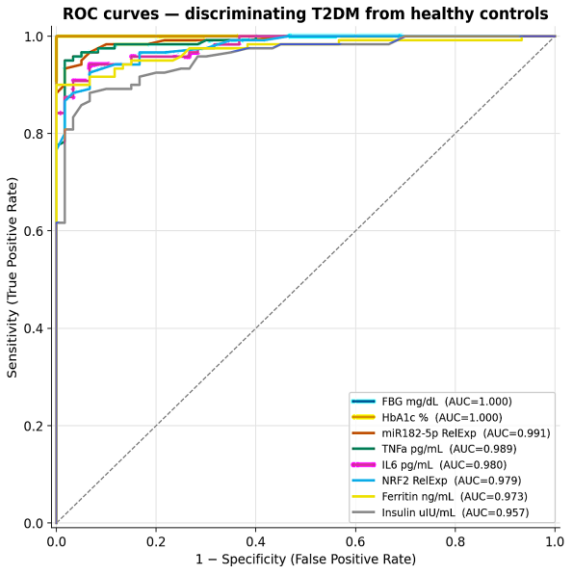

Figure 9: ROC curves for each biomarker discriminating T2DM from controls, ranked by AUC. Diagonal = chance (AUC = 0.5).

3.12. Predictors of poor glycemic control

Since the panel completely discriminated between T2DM and controls, a logistic diagnostic model was singular and was therefore not used, but instead a model of clinically relevant contrast: poorly controlled versus newly diagnosed T2DM (n = 120) was built. For univariate logistic regression, all markers were strong and significant predictors of poor control (Table 7, Figure 5). An increase by 1-SD in IL-6, TNF-α, miR-182-5p, and ferritin levels multiplied the odds of poor control by ~83-, ~32-, ~25-, and ~11-fold, respectively, while an increase by 1-SD in NRF2 level reduced the odds of poor control by ~90%. Age was not predictive (OR ≈ 1.07, p = 0.722). Near-perfect cross-validated discrimination (5-fold CV AUC = 0.996) was obtained when using a multivariable panel.

Table 11. Univariate logistic regression: odds of poorly controlled versus newly diagnosed T2DM per 1-SD increase in each marker (Wald 95% CI).

Predictor	OR per 1 SD	95% CI	p value	Direction
miR-182-5p (rel. exp.)	25.11	7.93 – 79.49	< 0.001	↑ risk
NRF2 (rel. exp.)	0.09	0.04 – 0.21	< 0.001	↓ protective
Ferritin ng/mL	11.09	4.78 – 25.69	< 0.001	↑ risk
IL-6 pg/mL	83.27	16.29 – 425.58	< 0.001	↑ risk
TNF-α pg/mL	32.23	9.32 – 111.43	< 0.001	↑ risk
Age	1.07	0.75 – 1.53	0.722	n.s.

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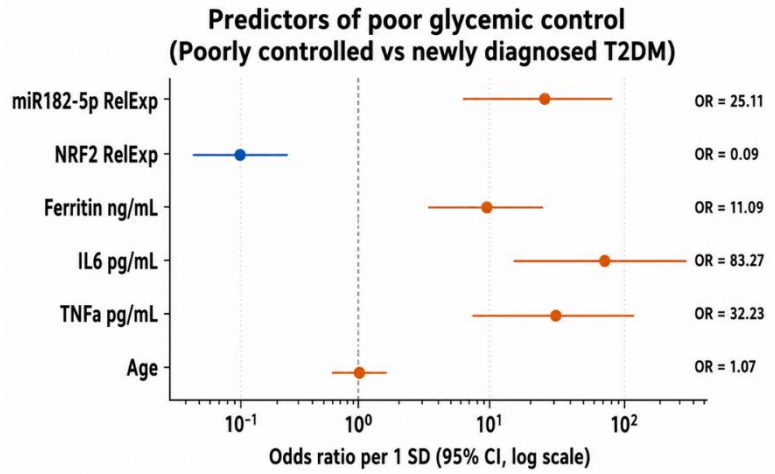

Figure 10: Forest plot of odds ratios (per 1 SD, log scale) for poor glycemic control. Orange = increased risk; NRF2 (blue) is protective. Bars = 95% CI.

3.13. Determinants of HbA1c

The multiple linear regression model that included the redox, iron, inflammatory and metabolic markers (plus age) predicted 90% of the variance in HbA1c ($R^2 = 0.900$, adjusted $R^2 = 0.896$; $F = 222.2$, $p < 0.001$; Table 8, Figure 6). Ferritin ($t = 4.98$, $p < 0.001$), miR-182-5p ($t = 3.18$, $p = 0.002$), IL-6 ($t = 3.77$, $p < 0.001$) and insulin ($t = 3.30$, $p = 0.001$) were independent predictors of HbA1c. The other markers were found to be stronger contributors with standardized coefficients of miR-182-5p ($\beta = 0.29$), ferritin ($\beta = 0.22$), and IL-6 ($\beta = 0.20$), whereas age and NRF2 were not independently significant after adjusting for these other markers.

Table 12. Multiple linear regression predicting HbA1c (%). Model $R^2 = 0.900$, adjusted $R^2 = 0.896$.

Predictor	B	Std. β	t	p value
Intercept	3.4791		2.31	0.022
miR-182-5p (rel. exp.)	1.5975	0.288	3.18	0.002
NRF2 (rel. exp.)	-1.1325	-0.098	-1.15	0.254
Ferritin ng/mL	0.0084	0.216	4.98	< 0.001
IL-6 pg/mL	0.1600	0.202	3.77	< 0.001
TNF-α pg/mL	0.0349	0.106	1.93	0.056
Insulin uIU/mL	0.0579	0.138	3.30	0.001
Age	-0.0061	-0.023	-0.94	0.346

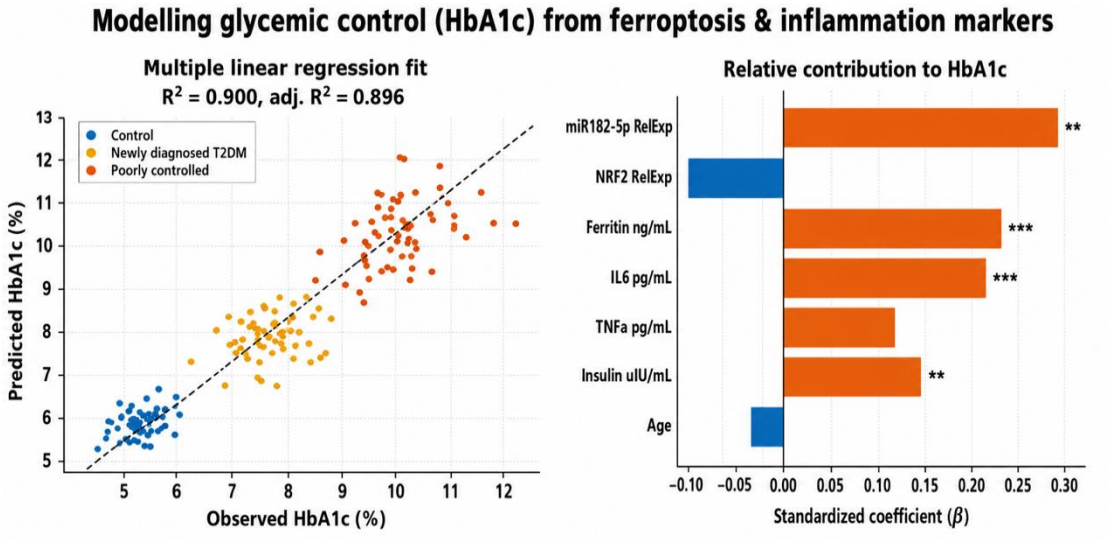

Figure 11: Left: predicted vs observed HbA1c coloured by group ($R^2 = 0.90$). Right: standardized coefficients ranking each predictor (* $p < 0.001$, ** $p < 0.01$, * $p < 0.05$).**

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IV. DISCUSSION

This study analyzed five associated markers in glycemic level stages. The expression of miR-182-5p increased with the progression of diabetes. The converse was true of NRF2. All three of these cytokines (ferritin, IL-6, and TNF-α) were all elevated as the disease progressed. The changes were evaluated on a scale of grading and found to be very significant. They suggest that there is a common iron–redox–inflammation axis in T2DM.

Our NRF2 result is consistent with previous reports. Diabetes frequently has low NRF2 activity. A low expression of NRF2 was observed in recent onset T2DM in India by Sireesh et al [19]. They also found that their patients had elevated levels of inflammatory cytokines [19]. This is the same reciprocity as that of us. A clinical trial from Iran further supports. Golpour and colleagues showed that NRF2 gene expression can be raised again by omega-3 supplements [20]. This indicates that NRF2 is a target that is modifiable. These results were further found in three distinct glycemic phases.

The increase in miR-182-5p is also concurrent with the literature. The miR-182-5p is dysregulated in diabetes. In a randomized trial in Sweden, plasma miR-182-5p levels were found to have changed with treatment of diabetes [21]. miR-182-5p has been detected in prediabetes and screen-detected diabetes in a South African study [22]. In Germany the researchers associated miR-182 with type 2 diabetes and fatty liver disease [23]. We have introduced a clear stepwise increase, with poor control, in our study. It also directly correlates this increase to the decrease in NRF2.

Our iron findings agree with regional and global studies. Glucose is the key to monitoring poor glycemic control, and high ferritin levels are a good indicator of that. One Saudi study correlated serum ferritin with glycemic control in patients with T2DM [24]. An Indian study has shown that there was an increase in ferritin levels in uncontrolled diabetes as compared to controlled diabetes [25]. A Chinese study found a link between ferritin and insulin resistance [26]. The inclusion of a large dose–response meta-analysis [27] supported ferritin as a risk marker for diabetes. This is consistent with our ferritin gradient. It also corroborates the concept of iron-dependent ferroptosis.

Our inflammatory test results are similar to many cohorts. In T2DM, levels of IL-6 and TNF-α increase. Iranian research revealed that IL-6 was associated with oxidative stress in newly diagnosed patients [28]. In diabetes, high levels of the inflammatory cytokines, TNF-α, IL-6, and CRP were reported in a study conducted in Kashmir, India [29]. A Thai cohort associated glycemic load with IL-6 and TNF-α [30]. These cytokines have been linked in a Pakistani study to insulin resistance [31]. Raised IL-6 and TNF-α was also observed in T2DM in an Iraqi study [32]. It is well recognized that TNF-α is a cause of insulin resistance [33]. Our data clearly indicate that both cytokines are increasing according to increasing severity.

Our work has additional meaning when seen in the context of the region. Diabetes is a huge burden in Asia and Middle East. A large national survey in India revealed a high and increasing burden [34]. High disease rates are reported in the Middle East and North Africa region as well [35]. This type of context provides molecular detail to our cohort. It reflects the correspondence between redox and iron markers and glycemia. This could be a clue to the rapid increase of complications in the area.

We have a number of strengths in our studies. It was able to measure multiple correlated markers simultaneously. It used three well-defined glycemic groups. It also gathered both clinical and molecular information. However, there are still some restrictions. The design was Cross sectional. So, it can't establish cause and effect. The sample was drawn from one placement. However, larger and longer studies are required in the future. The miR-182-5p/NRF2 connection should be tested directly using functional experiments.

V. CONCLUSION

Based upon the integrated clinical and molecular evidence gained in this study, the progressive deterioration of glycemic control in type 2 diabetes mellitus is associated with coordinated dysregulation of pathways of oxidative stress, iron metabolism, and inflammatory pathways. It was consistently found that the levels of miR-182-5p gradually increased while NRF2 was gradually decreased from healthy individuals to newly diagnosed and poorly controlled T2DM patients. Serum ferritin, IL-6 and TNF-α were all significantly elevated, and showed strong correlation to HbA1c and disease severity. Together the miR-182-5p/NRF2 association points to a role for antioxidant defense in chronic inflammation and iron-dependent oxidative injury in the development of T2DM. The excellent discriminatory power of these markers, as well as their high correlation, and their predictive ability for sub-optimal glycemic control, indicate that they form a biologically connected iron–redox–inflammation pathway rather than individual pathological events.

The results taken together suggest that a combination of the markers miR-182-5p, NRF2, ferritin, IL-6 and TNF-α could be of value for disease stratification, as well as monitoring glycemic deterioration and identifying patients with higher risk for progression to diabetes and associated complications. The cross-sectional study design does not allow for causal inference; however the findings provide a solid basis for further longitudinal studies and mechanistic studies that would confirm the miR-182-5p/NRF2 signaling pathway as a biomarker panel and a therapeutic target to manage type 2 diabetes mellitus with precision medicine.

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