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CORRELATIONAL ANALYSIS OF OXIDATIVE STRESS AND INSULIN RESISTANCE WITH G6PD ACTIVITY IN TYPE 2 DIABETICS: AN INSTITUTIONAL BASED STUDY

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, insulin resistance, and progressive metabolic derangements. Increasing evidence suggests that oxidative stress plays a pivotal role in the pathogenesis of insulin resistance and the development of diabetic complications. Glucose-6-phosphate dehydrogenase (G6PD), a key enzyme of the pentose phosphate pathway, is essential for maintaining cellular redox balance through the generation of NADPH. Reduced G6PD activity may impair antioxidant defenses and exacerbate oxidative stress, thereby contributing to worsening insulin resistance and poor glycemic control in patients with T2DM. the aim is to analyse and correlate Oxidative Stress and Insulin Resistance with G6PD Activity in Type 2 Diabetics.

Materials and Methods: This hospital-based analytical cross-sectional study included 96 adult patients with confirmed T2DM. Detailed clinical evaluation and anthropometric measurements were performed. Fasting venous blood samples were collected for estimation of fasting plasma glucose, HbA1c, lipid profile, serum insulin, oxidative stress markers [malondialdehyde (MDA), superoxide dismutase (SOD), and reduced glutathione (GSH)], and erythrocyte G6PD activity. Insulin resistance was assessed using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Patients were categorized based on G6PD activity status.

Results: The mean age of participants was 54.72 ± 8.91 years, with a male predominance (60.42%). Low G6PD activity was observed in 32.29% of patients. Individuals with low G6PD activity had significantly higher MDA levels and lower SOD and GSH levels, indicating increased oxidative stress. Fasting insulin levels, HOMA-IR, and HbA1c were also significantly higher in the low G6PD group compared to those with normal activity. G6PD activity showed a significant negative correlation with MDA, fasting insulin, HOMA-IR, and HbA1c, and a positive correlation with antioxidant markers.

Conclusion: Reduced erythrocyte G6PD activity in T2DM patients is associated with enhanced oxidative stress, increased insulin resistance, and poorer glycemic control. These findings underscore the importance of redox imbalance in the metabolic dysregulation of T2DM and suggest that G6PD activity may serve as a useful biomarker for identifying high-risk patients.

Keywords: Type 2 Diabetes Mellitus; Oxidative Stress; Insulin Resistance; Glucose-6-Phosphate Dehydrogenase; HOMA-IR.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common chronic metabolic disorders worldwide and represents a major public health challenge because of its high prevalence, long duration, and close association with disabling microvascular and macrovascular complications. The clinical burden of

T2DM extends beyond hyperglycemia to include obesity, hypertension, dyslipidemia, and progressive end-organ damage, which together increase morbidity, mortality, and health-care expenditure. In many low- and middle-income settings, tertiary care hospitals increasingly manage patients with long-standing diabetes, suboptimal metabolic control, and multiple comorbidities, making it important to explore biological pathways that contribute to disease severity and complications.[1]

A central pathophysiological hallmark of T2DM is insulin resistance, where insulin-responsive tissues—primarily skeletal muscle, liver, and adipose tissue—show reduced biological response to circulating insulin. This impaired signalling leads to decreased peripheral glucose uptake, increased hepatic glucose output, and compensatory hyperinsulinemia, which can persist for years before pancreatic β-cell function declines. In clinical research and routine metabolic profiling, insulin resistance is often estimated using surrogate indices derived from fasting measurements. The homeostasis model assessment (HOMA) remains one of the most widely used approaches because it provides a practical estimate of insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations.[2] In T2DM populations, higher HOMA-IR values generally reflect greater insulin resistance and are commonly associated with central obesity, dyslipidemia, and poor glycemic control. Alongside disordered glucose metabolism, oxidative stress has emerged as a key contributor to the initiation and progression of T2DM. Oxidative stress results from an imbalance between reactive oxygen species (ROS) generation and antioxidant defense capacity, culminating in oxidative modification of lipids, proteins, and nucleic acids. In diabetes, chronic hyperglycemia promotes ROS through multiple mechanisms, including glucose autoxidation, mitochondrial electron transport chain overload, advanced glycation end product formation, and activation of pro-oxidant enzymatic pathways. Over time, sustained oxidative stress can impair insulin signalling, damage β-cells (which possess relatively weak intrinsic antioxidant defenses), and accelerate vascular dysfunction. Recent comprehensive reviews describe oxidative stress as an important mechanistic bridge linking metabolic dysregulation to inflammation, endothelial dysfunction, and the development of diabetic complications.[3]

Because oxidative stress is not directly measurable as a single entity, studies frequently rely on biochemical markers that capture oxidant burden and antioxidant capacity. Lipid peroxidation products such as malondialdehyde (MDA) are commonly used to indicate oxidative damage to membrane lipids, while enzymatic and non-enzymatic antioxidants—such as superoxide dismutase (SOD) and reduced glutathione (GSH)—reflect the capacity to neutralize ROS and maintain redox homeostasis. Systematic evaluations of oxidative stress biomarkers in T2DM highlight that elevated lipid peroxidation and reduced antioxidant defenses are recurring patterns across diverse populations and are clinically relevant because they correlate with glycemic control, complication risk, and overall disease severity.[4] In clinical settings, these markers are attractive because they can be measured from accessible blood samples and may provide insight into biological vulnerability beyond traditional metabolic parameters. Oxidative stress and insulin resistance are closely interrelated, and the association appears to be bidirectional. Increased ROS can interfere with insulin signalling through oxidative modification of insulin receptor substrates, activation of stress-responsive kinases, and promotion of inflammatory pathways that blunt insulin action. Conversely, insulin resistance and hyperglycemia can amplify oxidative stress by increasing substrate flux through mitochondria and pro-oxidant metabolic pathways. Longitudinal and epidemiologic evidence supports a link between oxidative stress markers and insulin resistance indices, suggesting that oxidative injury is not merely a consequence of dysglycemia but may also contribute to the progression of metabolic dysfunction.[5]

This interdependence provides a rationale for simultaneously evaluating oxidative stress and insulin resistance when attempting to understand heterogeneity among patients with T2DM. Within this redox–metabolic framework, glucose-6-phosphate dehydrogenase (G6PD) holds particular relevance. G6PD is the rate-limiting enzyme of the oxidative arm of the pentose phosphate pathway, generating nicotinamide adenine dinucleotide phosphate in its reduced form (NADPH). NADPH is essential for maintaining reduced glutathione via glutathione reductase and for supporting multiple antioxidant systems that protect cells from oxidative injury. In erythrocytes, which lack mitochondria and depend heavily on the pentose phosphate pathway for NADPH production, adequate G6PD activity is critical to preserve membrane integrity and prevent oxidative hemolysis. Beyond erythrocytes, G6PD-dependent NADPH production influences cellular redox balance, biosynthetic reactions, and signalling pathways, and its regulation has been implicated in both neoplastic and non-neoplastic diseases. Recent work summarizing regulation of G6PD emphasizes that altered G6PD activity can reshape cellular vulnerability to oxidative stress and modify downstream metabolic signalling, reinforcing its potential importance in metabolic disorders such as T2DM.[6,7]

MATERIALS AND METHODS

This hospital-based, analytical and correlational cross-sectional study was conducted at Department of Biochemistry, SUM Hospital Campus 2, Bhubaneswar, Odisha, India.

The study aimed to evaluate oxidative stress and insulin resistance and to correlate these with erythrocyte glucose-6-phosphate dehydrogenase

(G6PD) activity among patients with type 2 diabetes mellitus (T2DM). A total of 96 patients diagnosed with T2DM were enrolled from outpatient and/or inpatient services of the tertiary care hospital. Diagnosis of T2DM was based on standard clinical criteria and/or documented evidence in medical records, including prior physician diagnosis and/or use of antidiabetic medications. Eligible participants were recruited using a consecutive sampling approach until the required sample size was achieved.

Eligibility Criteria

Adult patients with confirmed T2DM who provided written informed consent were included. Patients were excluded if they had conditions likely to influence oxidative stress markers, insulin resistance indices, or erythrocyte enzyme activity, such as acute infections or inflammatory conditions, chronic liver disease, chronic kidney disease (moderate to severe), hemolytic anemia or known hematological disorders, recent blood transfusion, malignancy, pregnancy, hypothyroidism/hyperthyroidism not controlled on treatment, or current intake of high-dose antioxidant supplements or drugs known to affect oxidative stress parameters. Individuals with known congenital G6PD deficiency diagnosis (if already documented) were not excluded a priori unless it interfered with analysis; rather, measured G6PD activity was used for categorization/interpretation as per laboratory reference ranges.

Methodology

All participants underwent a structured clinical evaluation including demographic details, duration and treatment history of diabetes, comorbidities, smoking/alcohol history, and current medications. Anthropometric measurements were recorded using standardized procedures: height (cm) and weight (kg) were measured to compute body mass index (BMI, kg/m²), and waist circumference (cm) was measured midway between the iliac crest and lower rib margin. Resting blood pressure was recorded using a calibrated sphygmomanometer, and an average of two readings was considered.

After an overnight fast of at least 8–12 hours, venous blood samples were collected under aseptic precautions. Samples were divided into appropriate tubes for plasma/serum separation and for whole blood/erythrocyte enzyme analysis. Fasting plasma glucose (FPG) and lipid profile (total cholesterol, triglycerides, HDL-C; LDL-C calculated or directly measured as per laboratory protocol) were analyzed using standard automated methods. Glycated hemoglobin (HbA1c) was measured using an NGSP-aligned method to assess glycemic control. Serum insulin was estimated by an immunoassay-based method available in the hospital laboratory, following the manufacturer's instructions and internal quality control procedures.

Insulin resistance was estimated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), calculated from fasting glucose and fasting insulin values using the formula: HOMA-IR = [Fasting insulin (μIU/mL) × Fasting plasma glucose (mg/dL)] / 405 (or equivalent SI-unit formula if glucose was analyzed in mmol/L). Higher HOMA-IR values were interpreted as greater insulin resistance. Where needed for additional interpretation, participants could be stratified into categories based on distribution (e.g., tertiles/median split) of HOMA-IR within the study population.

Oxidative stress was evaluated using established biochemical markers representing oxidant burden and/or antioxidant defense. Lipid peroxidation was assessed by measuring malondialdehyde (MDA) (commonly via thiobarbituric acid reactive substances method or an equivalent validated kit-based method), expressed in standard concentration units as per the assay. Antioxidant status was assessed using superoxide dismutase (SOD) activity and reduced glutathione (GSH) levels (or total antioxidant capacity if available), measured using validated spectrophotometric/kit-based methods under standardized laboratory conditions. All assays were performed with appropriate calibration, internal quality control, and adherence to the manufacturer's protocol or validated departmental SOPs to ensure reproducibility.

Erythrocyte G6PD activity was measured from whole blood using a quantitative method (spectrophotometric or kit-based), based on the rate of NADPH generation from $NADP^+$ in the presence of glucose-6-phosphate. Enzyme activity was expressed as U/g Hb or U/10^{12} RBC depending on the assay format, and interpreted using the laboratory's reference range. Hemoglobin estimation was performed to normalize G6PD activity where required. Participants were evaluated for distribution of G6PD activity and were also considered for subgroup analysis using laboratory cut-offs (e.g., low/normal activity) when appropriate.

The primary variables included erythrocyte G6PD activity, oxidative stress markers (MDA, SOD, GSH/total antioxidant capacity as applicable), fasting insulin, and HOMA-IR. Secondary variables included age, sex, BMI, waist circumference, blood pressure, HbA1c, fasting glucose, and lipid parameters. Data were recorded in a structured proforma and subsequently entered into an electronic database with verification to minimize entry errors.

Statistical Analysis

Data were analyzed using SPSS version 26.0. Continuous variables were tested for normality (e.g., Shapiro–Wilk test and visual inspection of histograms). Normally distributed data were presented as mean ± standard deviation, and non-normally distributed data were presented as median (interquartile range). Categorical variables were expressed as frequencies and percentages. The correlation between G6PD activity and oxidative stress markers and between G6PD activity and insulin resistance (HOMA-IR) was assessed using Pearson's correlation for normally distributed variables or Spearman's rank correlation for skewed variables. Comparisons of biochemical parameters across categories of G6PD activity (e.g., low vs normal, or

tertiles) were performed using independent sample t-test/ANOVA for parametric data and Mann–Whitney U/Kruskal–Wallis test for nonparametric data. To account for potential confounders, multivariable linear regression analysis was performed with oxidative stress markers and/or HOMA-IR as dependent variables and G6PD activity as an independent predictor while adjusting for clinically relevant covariates such as age, sex, BMI/waist circumference, HbA1c, and lipid parameters. A two-tailed p value < 0.05 was considered statistically significant.

RESULTS

[Table 1] Baseline Demographic and Clinical Characteristics

[Table 1] summarizes the baseline demographic and clinical profile of the 96 study participants with type 2 diabetes mellitus. The mean age of the study population was 54.72 ± 8.91 years, indicating a predominance of middle-aged and older adults. Males constituted a higher proportion of the cohort (60.42%) compared to females (39.58%), suggesting a male preponderance in the study sample. The mean body mass index was 27.84 ± 3.62 kg/m², reflecting that most participants were overweight or obese. Central obesity was also evident, as indicated by an increased mean waist circumference of 96.31 ± 8.74 cm. The mean systolic and diastolic blood pressure values were 132.58 ± 14.62 mmHg and 82.41 ± 8.93 mmHg, respectively, showing that a substantial proportion of patients had elevated blood pressure levels. Lifestyle risk factors were also common, with 30.21% of participants reporting smoking and 27.08% reporting alcohol consumption, both of which may contribute to metabolic dysregulation and oxidative stress.

[Table 2] Glycemic Profile, Lipid Parameters, Insulin Resistance, Oxidative Stress Markers and G6PD Activity

[Table 2] depicts the biochemical characteristics of the study population. The mean fasting plasma glucose level was 156.84 ± 34.92 mg/dL and the mean HbA1c was 8.24 ± 1.36%, indicating suboptimal glycemic control among the participants. The mean fasting insulin level was 18.62 ± 6.41 µIU/mL, with a corresponding mean HOMA-IR value of 7.19 ± 2.83, suggesting a high degree of insulin resistance in this cohort. The lipid profile showed elevated total cholesterol (198.46 ± 36.71 mg/dL) and triglycerides (176.53 ± 58.24 mg/dL), along with low HDL-C levels (39.18 ± 7.92 mg/dL), consistent with diabetic dyslipidemia. Oxidative stress assessment revealed increased lipid peroxidation as evidenced by elevated malondialdehyde levels (4.86 ± 1.32 nmol/mL). Antioxidant defense markers, including superoxide dismutase (2.91 ± 0.84 U/mL) and reduced glutathione (6.42 ± 1.71 mg/dL), showed comparatively lower levels, indicating compromised antioxidant capacity. The mean erythrocyte G6PD activity was 6.18 ± 1.92 U/g Hb, with a wide variation among participants.

Table 1: Baseline Demographic and Clinical Characteristics (n = 96)

Variable	Value
Age (years), mean ± SD	54.72 ± 8.91
Male, n (%)	58 (60.42%)
Female, n (%)	38 (39.58%)
Body Mass Index (kg/m²), mean ± SD	27.84 ± 3.62
Waist circumference (cm), mean ± SD	96.31 ± 8.74
Systolic BP (mmHg), mean ± SD	132.58 ± 14.62
Diastolic BP (mmHg), mean ± SD	82.41 ± 8.93
Smokers, n (%)	29 (30.21%)
Alcohol consumers, n (%)	26 (27.08%)

Table 2: Glycemic Profile, Lipid Parameters, Insulin Resistance, Oxidative Stress Markers and G6PD Activity

Parameter	Mean ± SD
Fasting plasma glucose (mg/dL)	156.84 ± 34.92
HbA1c (%)	8.24 ± 1.36
Fasting insulin (µIU/mL)	18.62 ± 6.41
HOMA-IR	7.19 ± 2.83
Total cholesterol (mg/dL)	198.46 ± 36.71
Triglycerides (mg/dL)	176.53 ± 58.24
HDL-C (mg/dL)	39.18 ± 7.92
LDL-C (mg/dL)	118.74 ± 29.36
Malondialdehyde (MDA, nmol/mL)	4.86 ± 1.32
Superoxide dismutase (SOD, U/mL)	2.91 ± 0.84
Reduced glutathione (GSH, mg/dL)	6.42 ± 1.71
G6PD activity (U/g Hb)	6.18 ± 1.92

Table 3: Distribution According to G6PD Activity Status

G6PD activity category	n (%)
Low G6PD activity	31 (32.29%)
Normal G6PD activity	65 (67.71%)
Total	96 (100.00%)

Table 4: Comparison of Oxidative Stress Markers and Insulin Resistance by G6PD Activity Status

Parameter	Low G6PD (n = 31) Mean ± SD	Normal G6PD (n = 65) Mean ± SD	p-value
MDA (nmol/mL)	5.62 ± 1.21	4.49 ± 1.18	<0.001
SOD (U/mL)	2.41 ± 0.62	3.14 ± 0.81	<0.001
GSH (mg/dL)	5.58 ± 1.32	6.82 ± 1.73	0.002
Fasting insulin (µIU/mL)	21.04 ± 6.93	17.44 ± 5.82	0.009
HOMA-IR	8.43 ± 2.91	6.61 ± 2.62	0.004
HbA1c (%)	8.71 ± 1.44	8.01 ± 1.28	0.018

Table 5: Correlation of G6PD Activity with Oxidative Stress Markers and Insulin Resistance (n = 96)

Variable	Correlation coefficient (r)	p-value
MDA	−0.52	<0.001
SOD	+0.47	<0.001
GSH	+0.41	<0.001
Fasting insulin	−0.36	<0.001
HOMA-IR	−0.44	<0.001
HbA1c	−0.29	0.004

[Table 3] Distribution According to G6PD Activity Status

As shown in [Table 3], participants were categorized based on erythrocyte G6PD activity. Low G6PD activity was observed in 31 patients (32.29%), while the remaining 65 patients (67.71%) had normal G6PD activity. This finding indicates that nearly one-third of the T2DM patients in the study exhibited reduced G6PD activity, suggesting a potentially important role of impaired redox metabolism in a significant proportion of the diabetic population.

[Table 4] Comparison of Oxidative Stress Markers and Insulin Resistance by G6PD Activity Status

[Table 4] compares oxidative stress parameters, insulin resistance indices, and glycemic control between patients with low and normal G6PD activity. Patients with low G6PD activity had significantly higher malondialdehyde levels (5.62 ± 1.21 vs. 4.49 ± 1.18 nmol/mL; $p < 0.001$), indicating increased oxidative stress. In contrast, antioxidant markers such as superoxide dismutase (2.41 ± 0.62 vs. 3.14 ± 0.81 U/mL; $p < 0.001$) and reduced glutathione (5.58 ± 1.32 vs. 6.82 ± 1.73 mg/dL; $p = 0.002$) were significantly lower in the low G6PD group. Furthermore, fasting insulin levels (21.04 ± 6.93 vs. 17.44 ± 5.82 µIU/mL; $p = 0.009$) and HOMA-IR values (8.43 ± 2.91 vs. 6.61 ± 2.62; $p = 0.004$) were significantly higher in patients with low G6PD activity, reflecting greater insulin resistance. Glycemic control was also poorer in this group, as demonstrated by significantly higher HbA1c levels (8.71 ± 1.44 vs. 8.01 ± 1.28%; $p = 0.018$).

[Table 5] Correlation of G6PD Activity with Oxidative Stress Markers and Insulin Resistance

[Table 5] presents the correlation analysis between erythrocyte G6PD activity and key metabolic and oxidative stress parameters. G6PD activity showed a strong negative correlation with malondialdehyde levels ($r = −0.52$, $p < 0.001$), indicating that lower G6PD activity was associated with higher oxidative stress. Conversely, significant positive correlations were observed between G6PD activity and antioxidant markers, including superoxide dismutase ($r = +0.47$, $p < 0.001$) and reduced glutathione ($r = +0.41$, $p < 0.001$). Additionally, G6PD activity demonstrated significant negative correlations with fasting insulin levels ($r = −0.36$, $p < 0.001$) and HOMA-IR ($r = −0.44$, $p < 0.001$), suggesting that reduced G6PD activity is linked to increased insulin resistance. A modest but significant negative correlation was also noted between G6PD activity and HbA1c ($r = −0.29$, $p = 0.004$), indicating poorer long-term glycemic control in individuals with lower G6PD activity.

DISCUSSION

The present tertiary-care, hospital-based study included 96 T2DM patients with a mean age of 54.72 ± 8.91 years and an overweight phenotype (BMI 27.84 ± 3.62 kg/m², waist circumference 96.31 ± 8.74 cm), suggesting a population with high cardiometabolic risk. In contrast, Akter et al. (2010) studied female T2DM patients aged ~46 years (46.17–46.23 years) with comparatively lower BMI (~25.50–25.59 kg/m²) than our cohort, indicating our participants were older and more adipose—two factors known to amplify oxidative stress and worsen insulin resistance, potentially intensifying the observed redox–metabolic disturbances in our setting.[8]

A key observation was that 31/96 (32.29%) participants had low erythrocyte G6PD activity, implying that nearly one-third of our T2DM population may have compromised NADPH-generating capacity. This proportion is higher than that reported by Ahmed et al. (2022) from Sudan, where low G6PD activity occurred in 21.6% (53/245) of diabetic patients (and none in controls), and low activity showed a significant association with hyperglycemia. Differences in ethnicity, background genetic prevalence, assay cut-offs, and recruitment setting (tertiary-care vs mixed) may explain why the frequency of low activity was higher in our cohort.[9]

Our biochemical profile demonstrated poor glycemic control (FPG 156.84 ± 34.92 mg/dL; HbA1c 8.24 ± 1.36%) along with increased oxidative burden (MDA 4.86 ± 1.32 nmol/mL) and reduced antioxidant defenses (SOD and GSH levels). The direction and

magnitude of lipid peroxidation are comparable to Singh et al. (2015), where MDA in T2DM patients without microvascular complications was 4.01 ± 0.22 µmol/L, while those with microvascular complications had 6.08 ± 0.47 µmol/L, indicating a graded rise in lipid peroxidation with complication burden. Their study also reported a positive association between MDA and HbA1c, aligning with our finding that poorer glycemia (higher HbA1c) clustered with worse redox status.[10]

When stratified by G6PD status, our data clearly showed a redox disadvantage in the low-G6PD group: higher MDA (5.62 ± 1.21 vs 4.49 ± 1.18; $p < 0.001$) with significantly lower SOD (2.41 ± 0.62 vs 3.14 ± 0.81; $p < 0.001$) and lower GSH (5.58 ± 1.32 vs 6.82 ± 1.73; $p = 0.002$). A similar oxidative stress pattern has been reported in complication-focused cohorts; for example, Hou et al. (2021) observed that T2DM with complications exhibited higher lipid peroxidation (MDA ~5.96 µmol/L) along with reduced antioxidant activity (SOD reported as ~660.96 U/gHb in the complication group), reinforcing that oxidative injury and reduced antioxidant defense coexist in more severe diabetic phenotypes—even though absolute units and matrices differ from ours.[11]

Insulin resistance was substantially worse in patients with low G6PD activity in our study (fasting insulin 21.04 ± 6.93 vs 17.44 ± 5.82 µIU/mL; $p = 0.009$, HOMA-IR 8.43 ± 2.91 vs 6.61 ± 2.62; $p = 0.004$), supporting a clinically meaningful metabolic link between diminished G6PD activity and insulin resistance. Mechanistic metabolic work, however, highlights tissue-specific behavior of G6PD: Park et al. (2005) showed that G6PD expression increased markedly in obese mouse adipose tissue (e.g., ~2.9-fold in subcutaneous and ~6.3-fold in epididymal fat in db/db mice) and that experimental overexpression increased adipocyte G6PD activity (~1.4-fold) with impaired insulin-dependent glucose uptake—suggesting that excess G6PD within lipogenic tissues may drive insulin resistance, whereas reduced erythrocyte G6PD may primarily reflect impaired antioxidant buffering; both pathways can converge on oxidative stress and insulin signaling failure, explaining why directionality can differ by tissue and disease context.[12]

Our correlation analysis strengthens the biological coherence of these findings: G6PD activity correlated negatively with MDA ($r = -0.52$; $p < 0.001$) and insulin resistance (HOMA-IR $r = -0.44$; $p < 0.001$) and positively with antioxidants (SOD $r = +0.47$; $p < 0.001$; GSH $r = +0.41$; $p < 0.001$). This "lower G6PD–higher oxidative stress" relationship is consistent with broader clinical evidence. In the meta-analysis by Banik et al. (2021), oxidative stress biomarkers in T2DM showed substantially higher lipid peroxidation, with pooled results demonstrating significantly elevated MDA (standardized mean difference ~2.27, 95% CI reported in the paper), supporting that our observed mean MDA and the stronger oxidative phenotype in the low-G6PD subgroup fit within the wider T2DM oxidative stress landscape.[13]

Clinically, the degree of hyperglycemia in our cohort indicates a sizable burden of sustained dysglycemia: overall HbA1c was 8.24 ± 1.36%, and it was significantly higher in low-G6PD patients (8.71 ± 1.44%) than normal-G6PD (8.01 ± 1.28%, $p = 0.018$). This is important because persistent hyperglycemia thresholds are commonly used to define higher-risk strata; for example, Ye et al. (2016) categorized persistent hyperglycemia at HbA1c ≥ 9.0%, demonstrating biochemical alterations at higher HbA1c states. In our study, the low-G6PD subgroup mean HbA1c (8.71%) approaches this high-risk band, supporting the interpretation that reduced G6PD activity may cluster with clinically meaningful deterioration in long-term glycemic exposure.[14]

From a pathophysiological standpoint, our results support a model in which reduced G6PD activity compromises NADPH availability, weakens glutathione recycling, increases lipid peroxidation, and thereby aggravates insulin resistance and glycemic dysregulation—consistent with established mechanistic frameworks linking oxidative stress to diabetic complications. Tiwari et al. (2013) emphasized that diabetic oxidative stress is reflected by increased lipid peroxidation markers such as MDA and weakening antioxidant defenses (including glutathione-dependent systems), which conceptually aligns with our findings of higher MDA and lower antioxidant markers in the low-G6PD group, and with the strong correlations showing that lower G6PD tracks with both oxidative stress and insulin resistance in our cohort.[15]

CONCLUSION

This study demonstrates that reduced erythrocyte G6PD activity is common among patients with type 2 diabetes mellitus and is significantly associated with increased oxidative stress and greater insulin resistance. Patients with low G6PD activity exhibited higher lipid peroxidation, diminished antioxidant defenses, and poorer glycemic control compared to those with normal G6PD activity. The significant correlations observed between G6PD activity, oxidative stress markers, and HOMA-IR highlight the important role of impaired redox homeostasis in the metabolic dysregulation of T2DM. Assessment of G6PD activity alongside oxidative stress and insulin resistance parameters may help identify high-risk diabetic patients who could benefit from targeted therapeutic and preventive strategies.

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