International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Association of Serum Oxidative Stress Markers and Antioxidant Status with Glycaemic Control in Patients with Type 2 Diabetes Mellitus

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OPEN ACCESS

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Received: 13-01-2026
Accepted: 30-01-2026
Available online: 16-02-2026

ABSTRACT

Background: Oxidative stress plays a pivotal role in the pathogenesis and progression of Type 2 Diabetes Mellitus (T2DM) and its complications. Poor glycaemic control enhances reactive oxygen species generation and compromises antioxidant defenses.
Objectives: To evaluate the association between serum oxidative stress markers and antioxidant status with glycaemic control in patients with T2DM.
Methods: This hospital-based cross-sectional original study included 150 patients with T2DM attending outpatient and inpatient services between January and December 2025. Glycaemic control was assessed using glycated hemoglobin (HbA1c). Serum oxidative stress markers—malondialdehyde (MDA)—and antioxidant parameters—superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), vitamin C, and vitamin E—were measured using standardized biochemical methods. Participants were categorized into good and poor glycaemic control groups based on HbA1c (<7% and ≥7%). Statistical analysis included Student's t-test, Pearson correlation, and multivariate regression.
Results: Patients with poor glycaemic control exhibited significantly higher MDA levels and lower antioxidant enzyme activities compared to those with good glycaemic control ($p<0.001$). HbA1c showed a positive correlation with MDA and negative correlations with SOD, catalase, GPx, vitamin C, and vitamin E. Oxidative stress markers remained independently associated with HbA1c after adjusting for confounders.
Conclusion: Poor glycaemic control in T2DM is significantly associated with increased oxidative stress and reduced antioxidant defenses. Monitoring oxidative stress markers along with glycaemic indices may help in early identification of patients at higher risk of complications.

Keywords*: Type 2 Diabetes Mellitus, Oxidative Stress, Antioxidants, Glycaemic Control, HbA1c.*

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a complex, chronic metabolic disorder characterized by persistent hyperglycemia resulting from a combination of insulin resistance and relative insulin deficiency.[1] It represents one of the most significant non-communicable diseases worldwide, with a rapidly rising prevalence, particularly in low- and middle-income countries. The growing burden of T2DM is associated with substantial morbidity, mortality, and healthcare costs, primarily due to its long-term microvascular and macrovascular complications.[2]

Chronic hyperglycemia is the central biochemical abnormality in T2DM and is known to trigger multiple metabolic and cellular derangements. One of the most important mechanisms linking hyperglycemia to tissue damage is oxidative stress. Oxidative stress arises due to an imbalance between the generation of reactive oxygen species (ROS) and the capacity of antioxidant defense systems to neutralize them. [3] In diabetes, excessive glucose undergoes auto-oxidation and

non-enzymatic glycation, leading to increased ROS production through pathways such as the polyol pathway, protein kinase C activation, hexosamine pathway flux, and formation of advanced glycation end products. [4]

Reactive oxygen species, including superoxide anion, hydrogen peroxide, and hydroxyl radicals, can damage cellular lipids, proteins, and nucleic acids. Lipid peroxidation of cell membranes is a key consequence of oxidative stress, and malondialdehyde (MDA) is a well-established biomarker reflecting the extent of lipid peroxidation. Elevated MDA levels have been consistently reported in patients with diabetes and are associated with endothelial dysfunction, inflammation, and progression of diabetic complications. [5,6]

To counteract oxidative stress, the human body is equipped with an intricate antioxidant defense system comprising enzymatic antioxidants such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), as well as non-enzymatic antioxidants including vitamins C and E. Superoxide dismutase catalyzes the dismutation of superoxide radicals into hydrogen peroxide, which is subsequently decomposed by catalase and GPx. Vitamin C acts as a potent water-soluble antioxidant, while vitamin E protects membrane lipids from peroxidative damage. In T2DM, prolonged oxidative stress may overwhelm these protective mechanisms, resulting in depletion or reduced activity of antioxidants. [7] Glycated hemoglobin (HbA1c) is a reliable indicator of long-term glycaemic control and reflects average blood glucose levels over the preceding two to three months. [8] Poor glycaemic control, as indicated by elevated HbA1c levels, has been strongly associated with an increased risk of diabetic complications. Emerging evidence suggests that worsening glycaemic control is closely linked to enhanced oxidative stress and compromised antioxidant status, thereby accelerating cellular damage and disease progression. [9]

Despite extensive research, the relationship between oxidative stress markers, antioxidant status, and glycaemic control remains an area of active investigation, particularly in different population settings. Understanding this association is clinically important, as it may provide insights into the pathophysiology of diabetes and highlight the potential role of antioxidant strategies as adjuncts to glycaemic management. Therefore, the present study was undertaken to evaluate the association of serum oxidative stress markers and antioxidant status with glycaemic control in patients with Type 2 Diabetes Mellitus.[10]

OBJECTIVES

1. To estimate serum levels of oxidative stress marker (malondialdehyde) in patients with T2DM.
2. To assess antioxidant status (SOD, catalase, GPx, vitamin C, and vitamin E) in T2DM patients.
3. To determine the association between oxidative stress, antioxidant parameters, and glycaemic control as measured by HbA1c.

MATERIALS AND METHODS

Study Design and Setting: This hospital-based cross-sectional original research study was conducted in the Department of Biochemistry in collaboration with the Department of Medicine at a tertiary care teaching hospital.

Study Period: January 2025 to December 2025.

Study Population: A total of 150 diagnosed cases of Type 2 Diabetes Mellitus attending outpatient and inpatient services during the study period were enrolled.

Inclusion Criteria

- Patients aged 30–70 years.
- Diagnosed cases of T2DM as per ADA criteria.
- Patients on stable antidiabetic therapy for at least 3 months.

Exclusion Criteria

- Type 1 diabetes mellitus.
- Acute or chronic infections, inflammatory diseases, or malignancy.
- Chronic liver or renal disease.
- Patients on antioxidant supplementation.
- Smokers and chronic alcoholics.

Sample Size

A total of 150 cases were included based on feasibility and previous literature demonstrating adequate power to detect differences in oxidative stress parameters.

Data Collection

Detailed clinical history including age, sex, duration of diabetes, treatment modality, and anthropometric measurements were recorded. After overnight fasting, venous blood samples were collected under aseptic precautions.

Biochemical Parameters

- **Fasting Plasma Glucose (FPG):** Enzymatic glucose oxidase-peroxidase method.
- **HbA1c:** High-performance liquid chromatography (HPLC).
- **Malondialdehyde (MDA):** Thiobarbituric acid reactive substances (TBARS) method.
- **Superoxide Dismutase (SOD):** Spectrophotometric method.
- **Catalase:** Decomposition rate of hydrogen peroxide.
- **Glutathione Peroxidase (GPx):** NADPH oxidation method.
- **Vitamin C:** Colorimetric method.
- **Vitamin E:** Spectrophotometric method.

Grouping Based on Glycaemic Control

- **Good glycaemic control:** HbA1c <7%.
- **Poor glycaemic control:** HbA1c ≥7%.

Statistical Analysis

Data were analyzed using SPSS software (version 26). Continuous variables were expressed as mean ± standard deviation. Comparison between groups was done using Student's t-test. Pearson correlation coefficient assessed relationships between HbA1c and oxidative stress/antioxidant parameters. Multivariate linear regression was performed to identify independent associations. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of the Study Participants

Parameter	Mean ± SD / n (%)
Number of participants	150
Age (years)	54.2 ± 8.6
Male	82 (54.7%)
Female	68 (45.3%)
Duration of diabetes (years)	7.4 ± 3.1
BMI (kg/m²)	26.1 ± 3.4
Fasting plasma glucose (mg/dL)	156.8 ± 38.5
HbA1c (%)	8.1 ± 1.4

Table 1 summarizes the baseline demographic and clinical profile of the 150 patients with Type 2 Diabetes Mellitus included in the study. The mean age of the participants was 54.2 ± 8.6 years, indicating that the study population predominantly consisted of middle-aged adults. There was a slight male predominance, with 82 (54.7%) males and 68 (45.3%) females.

The mean duration of diabetes was 7.4 ± 3.1 years, suggesting that most participants had established disease rather than newly diagnosed diabetes. The average body mass index (BMI) was 26.1 ± 3.4 kg/m², reflecting an overweight population, which is a known risk factor for insulin resistance and poor glycaemic control.

Biochemically, the mean fasting plasma glucose level was 156.8 ± 38.5 mg/dL, indicating suboptimal glycaemic control in the study cohort. This finding was further supported by the mean HbA1c value of 8.1 ± 1.4%, which reflects poor long-term glycaemic control in a majority of participants. Overall, the table highlights that the study population comprised patients with moderately long-standing diabetes and inadequate glycaemic control, providing a suitable cohort for assessing the association between oxidative stress, antioxidant status, and glycaemic control.

Table 2: Comparison of Oxidative Stress Marker and Antioxidant Parameters Based on Glycaemic Control

Parameter	Good Glycaemic Control (HbA1c <7%, n=58)	Poor Glycaemic Control (HbA1c ≥7%, n=92)	p-value
MDA (nmol/mL)	2.8 ± 0.6	4.1 ± 0.9	<0.001
SOD (U/mL)	5.6 ± 1.1	3.9 ± 0.8	<0.001
Catalase (kU/L)	62.4 ± 10.2	48.7 ± 9.6	<0.001
GPx (U/L)	41.8 ± 7.5	30.2 ± 6.8	<0.001
Vitamin C (mg/dL)	1.12 ± 0.21	0.74 ± 0.18	<0.001
Vitamin E (mg/dL)	1.04 ± 0.19	0.69 ± 0.16	<0.001

Table 2 compares serum oxidative stress marker and antioxidant parameters between patients with good glycaemic control (HbA1c <7%) and poor glycaemic control (HbA1c ≥7%). A statistically significant difference was observed between the two groups for all parameters studied.

Patients with poor glycaemic control demonstrated significantly higher levels of malondialdehyde (MDA) (4.1 ± 0.9 nmol/mL) compared to those with good glycaemic control (2.8 ± 0.6 nmol/mL), indicating increased lipid peroxidation and oxidative stress in the poorly controlled diabetic group (p <0.001).

Conversely, antioxidant enzyme activities were markedly reduced in patients with poor glycaemic control. Levels of superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) were significantly lower in the poor glycaemic control group compared to the good control group (p <0.001 for all), suggesting compromised enzymatic antioxidant defense in the presence of chronic hyperglycemia.

Similarly, non-enzymatic antioxidants vitamin C and vitamin E were significantly decreased in patients with poor glycaemic control, reflecting depletion of antioxidant reserves due to sustained oxidative stress. Overall, the table highlights a clear association between worsening glycaemic control and increased oxidative stress accompanied by reduced antioxidant status in patients with Type 2 Diabetes Mellitus.

Table 3: Correlation Between HbA1c and Oxidative Stress/Antioxidant Parameters

Parameter	Correlation coefficient (r)	p-value
MDA	0.62	<0.001
SOD	−0.55	<0.001
Catalase	−0.48	<0.001
GPx	−0.51	<0.001
Vitamin C	−0.46	<0.001
Vitamin E	−0.44	<0.001

Table 3 illustrates the Pearson correlation analysis between glycated hemoglobin (HbA1c) and serum oxidative stress as well as antioxidant parameters in patients with Type 2 Diabetes Mellitus. All correlations observed were statistically highly significant (p <0.001).

A strong positive correlation was found between HbA1c and malondialdehyde (MDA) (r = 0.62), indicating that increasing levels of long-term glycaemic exposure are associated with enhanced lipid peroxidation and oxidative stress.
In contrast, significant negative correlations were observed between HbA1c and all measured antioxidant parameters. HbA1c showed inverse correlations with superoxide dismutase (SOD) (r = −0.55), catalase (r = −0.48), and glutathione peroxidase (GPx) (r = −0.51), suggesting that worsening glycaemic control is associated with reduced enzymatic antioxidant activity.

Similarly, non-enzymatic antioxidants vitamin C (r = −0.46) and vitamin E (r = −0.44) also demonstrated significant negative correlations with HbA1c, reflecting depletion of antioxidant reserves with poor glycaemic control. Overall, this table emphasizes the close relationship between sustained hyperglycemia, increased oxidative stress, and diminished antioxidant defenses in Type 2 Diabetes Mellitus.

Table 4: Multivariate Linear Regression Analysis Showing Independent Predictors of Poor Glycaemic Control (HbA1c)

Variable	β coefficient	Standard Error	p-value
MDA	0.38	0.07	<0.001
SOD	−0.31	0.09	0.002
GPx	−0.27	0.08	0.004
Vitamin C	−0.21	0.06	0.008

Table 4 presents the results of multivariate linear regression analysis performed to identify independent predictors of glycaemic control, as measured by HbA1c, after adjusting for potential confounding variables.

Malondialdehyde (MDA) showed a significant positive association with HbA1c (β = 0.38, p <0.001), indicating that higher oxidative stress independently predicts poorer glycaemic control. This suggests that increased lipid peroxidation is strongly linked to sustained hyperglycemia, irrespective of other factors.

In contrast, antioxidant parameters demonstrated significant inverse associations with HbA1c. Superoxide dismutase (SOD) (β = −0.31, p = 0.002) and glutathione peroxidase (GPx) (β = −0.27, p = 0.004) emerged as independent negative predictors, indicating that higher enzymatic antioxidant activity is associated with better glycaemic control.

Similarly, the non-enzymatic antioxidant vitamin C showed a significant inverse relationship with HbA1c ($\beta = -0.21$, $p = 0.008$), suggesting a protective role against hyperglycemia-induced oxidative stress.

Overall, this table confirms that oxidative stress and antioxidant depletion are independently associated with poor glycaemic control in patients with Type 2 Diabetes Mellitus, reinforcing the importance of oxidative balance in diabetes management.

DISCUSSION

The baseline demographic and clinical characteristics observed in **Table 1** are largely consistent with findings reported in earlier studies on patients with Type 2 Diabetes Mellitus (T2DM).

The **mean age of 54.2 ± 8.6 years** in the present study aligns with several Indian and international studies, which have reported the majority of T2DM patients to be in the fifth and sixth decades of life. Studies by **Maritim et al**[8] and **Ceriello et al**[9] similarly documented mean ages ranging between 50 and 60 years, reflecting the progressive nature of T2DM and delayed diagnosis in many populations.

A **slight male predominance (54.7%)** observed in this study is comparable to reports from hospital-based studies in India and other developing countries, where male participation typically ranges from 52% to 60%. This gender distribution has been attributed to differences in healthcare-seeking behavior and lifestyle-related risk factors among males.

The **mean duration of diabetes (7.4 ± 3.1 years)** is comparable to findings from studies that included patients with established diabetes rather than newly diagnosed cases. Similar durations have been reported in studies assessing oxidative stress in T2DM, suggesting that prolonged exposure to hyperglycemia plays a significant role in oxidative imbalance.

The **mean BMI of 26.1 ± 3.4 kg/m²** indicates an overweight study population, which is consistent with previous literature highlighting obesity and overweight as common features among patients with T2DM. Comparable BMI values have been reported in Asian populations, where diabetes often occurs at lower BMI thresholds due to increased visceral adiposity.

The observed **mean fasting plasma glucose level of 156.8 ± 38.5 mg/dL** and **mean HbA1c of 8.1 ± 1.4%** are similar to those reported in studies focusing on glycaemic control and oxidative stress, where poor or suboptimal glycaemic control was common among study participants. Several studies have documented mean HbA1c values above 8%, underscoring the challenge of achieving optimal glycaemic targets in routine clinical practice. [8,9]

Overall, the findings of **Table 1** are in agreement with previously published studies and reflect a representative cohort of middle-aged, overweight individuals with long-standing and inadequately controlled Type 2 Diabetes Mellitus. This comparability supports the external validity of the present study and strengthens the relevance of its conclusions regarding oxidative stress and antioxidant status in relation to glycaemic control.

The correlation analysis presented in **Table 2** demonstrates a significant relationship between long-term glycaemic control (HbA1c) and oxidative stress as well as antioxidant status in patients with Type 2 Diabetes Mellitus (T2DM). These findings are in close agreement with results reported in several previous studies.

The **strong positive correlation between HbA1c and malondialdehyde (MDA) (r = 0.62)** observed in the present study is consistent with earlier reports indicating increased lipid peroxidation with worsening glycaemic control. Studies by **Maritim et al**[8] and **Bandeira et al**[11] documented similar positive correlations between HbA1c and MDA, suggesting that chronic hyperglycemia enhances oxidative damage to cellular lipids.

The **negative correlation between HbA1c and superoxide dismutase (SOD) (r = −0.55)** parallels findings from studies conducted by **Gupta et al**[12] and **Ceriello et al**[9]., where reduced SOD activity was significantly associated with poor glycaemic control. This decline in SOD activity may be attributed to increased utilization and glycation-induced inactivation of antioxidant enzymes in hyperglycaemic states.

Similarly, the **inverse relationships between HbA1c and catalase (r = −0.48) and glutathione peroxidase (GPx) (r = −0.51)** are comparable to observations from multiple clinical studies that reported diminished antioxidant enzyme activities in patients with poorly controlled diabetes. These findings support the concept that persistent oxidative stress leads to depletion of endogenous antioxidant defenses.

The **negative correlations of HbA1c with non-enzymatic antioxidants vitamin C (r = −0.46) and vitamin E (r = −0.44)** are also in agreement with previous studies, which have shown reduced plasma levels of these vitamins in patients with higher HbA1c values. Decreased concentrations of vitamins C and E have been linked to increased oxidative burden and impaired antioxidant recycling in diabetes.

Overall, the correlation patterns observed in the present study are consistent with existing literature and reinforce the hypothesis that poor glycaemic control is associated with increased oxidative stress and diminished antioxidant capacity. These similarities across studies strengthen the validity of the present findings and emphasize the clinical relevance of oxidative stress in the pathophysiology of Type 2 Diabetes Mellitus.

The present study demonstrates a strong association between poor glycaemic control and increased oxidative stress in patients with T2DM. Elevated MDA levels indicate enhanced lipid peroxidation due to excessive ROS production in hyperglycaemic states. Reduced activities of antioxidant enzymes observed in poorly controlled diabetics suggest depletion of defense mechanisms against oxidative damage. Chronic hyperglycemia may downregulate antioxidant enzyme synthesis or increase their utilization. The significant correlations between HbA1c and oxidative stress markers highlight the role of sustained hyperglycemia in promoting oxidative damage. These findings are consistent with previous studies that reported increased oxidative stress and diminished antioxidant capacity in uncontrolled diabetes.

CONCLUSION

- Poor glycaemic control in patients with Type 2 Diabetes Mellitus is significantly associated with increased oxidative stress and reduced antioxidant status. Incorporating oxidative stress markers alongside routine glycaemic monitoring may aid in early identification of patients at higher risk for diabetic complications and guide antioxidant-based therapeutic strategies.
- Assessment of oxidative stress parameters may provide additional insight into metabolic control and risk stratification for diabetic complications.

Acknowledgements
The authors acknowledge the support of the Department of Medicine and the central laboratory staff for their assistance in sample collection and biochemical analysis.

Conflict of Interest
None declared.

Funding
No external funding was received for this study.

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