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Serum Oxidative Stress Biomarkers and Antioxidant Enzyme Activity as Predictors of Cardiovascular Risk in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Cardiovascular disease (CVD) continues to be the leading contributor to illness and death in people with type 2 diabetes mellitus (T2DM). Oxidative stress has been recognized as a central factor in vascular damage, but its usefulness as a predictive marker through measurable biochemical indicators and antioxidant enzyme activity remains underexplored in South Asian populations.

Objective: This study aimed to investigate the link between cardiovascular risk and circulating oxidative stress biomarkers together with antioxidant enzyme activity in patients with T2DM.

Methods: A cross-sectional analysis was undertaken in three tertiary care hospitals in Pakistan, from March 2023 to January 2025. A total of 120 adults with T2DM, aged 35–70 years and living with the disease for at least five years, were included. The Framingham Risk Score was used to assess cardiovascular risk, and individuals were classified as either high risk or low–moderate risk. Serum malondialdehyde (MDA), protein carbonyls (PC), and advanced oxidation protein products (AOAPs) were used to quantify the oxidative stress. The levels of glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) were measured to assess the antioxidant defense. Additional investigations were also out, including lipid profiles, glycated hemoglobin (HbA1c), and high-sensitivity C-reactive protein.

Results: Out of the total participants, 52 (43.3%) were classified as high risk. Individuals had substantially greater levels of MDA (5.4 ± 1.1 vs. 3.2 ± 0.7 nmol/mL; $p < 0.001$), PC (2.6 ± 0.5 vs. 1.8 ± 0.4 nmol/mg; $p = 0.002$), and AOPPs (92.1 ± 15.6 vs. 68.4 ± 12.3 µmol/L; $p < 0.001$). The high-risk group had substantially reduced antioxidant enzyme activity for SOD (5.1 ± 1.0 vs. 7.2 ± 1.3 U/mL; $p < 0.001$), CAT (33.8 ± 5.9 vs. 42.5 ± 6.2 kU/L; $p < 0.01$), and GPx (49.5 ± 7.2 vs. 62.7 ± 8.4 U/mL; $p < 0.01$). Regression analysis showed that elevated cardiovascular risk was independently predicted by higher MDA (OR 2.9, 95% CI 1.8-4.5; $p < 0.001$) and decreased SOD activity (OR 2.3, 95% CI 1.4-3.9; $p = 0.002$).

Conclusion: Patients with T2DM who are at greater cardiovascular risk display higher oxidative stress and reduced antioxidant enzyme defense. The inclusion of these biomarkers in clinical evaluation may refine cardiovascular risk prediction and guide targeted preventive measures.

Keywords: Type 2 diabetes, cardiovascular risk, oxidative stress, biomarkers, antioxidant defence.

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INTRODUCTION

Diabetes mellitus, type 2 (T2DM) has now been identified as a severe health issue of the population at the global level and its prevalence in both industrialized countries and developing ones is increasing rapidly [1]. Current statistics provided by the International Diabetes Federation (IDF) have shown that more than 530 million individuals in the world have diabetes, most of whom have T2DM and it is expected that the number will continue to increase by 2045 by a substantial margin. Most of this burden falls on South Asia with Pakistan being one of the countries that have high levels. The pandemic is affected by urbanization, a lack of physical exercises, dietary modification, and genetic susceptibility [2].

Cardiovascular disease (CVD) is the most severe and common consequence of type 2 diabetes, accounting for a significant part of morbidity and death. It is estimated that people with diabetes are two to four times more likely than those without the condition to have peripheral vascular disease, cerebrovascular accidents, and coronary artery disease [3]. The combination of traditional cardiometabolic risk factors, including obesity, hypertension, dyslipidemia, and chronic hyperglycemia, with the additional load of oxidative stress results in this heightened sensitivity.

When reactive oxygen species (ROS) exceed the body's antioxidant defenses, oxidative stress results. Through processes including endothelial dysfunction, low-grade inflammation, vascular smooth muscle proliferation, and plaque instability, prolonged hyperglycemia in type 2 diabetes leads to oxidative damage, which worsens atherosclerosis. Advanced glycation end products (AGEs) and mitochondrial anomalies intensify oxidative damage, delaying vascular damage and increasing cardiovascular risk [4,5].

Several circulating indicators show detectable signs of oxidative stress. Malondialdehyde (MDA), a lipid peroxidation byproduct, indicates oxidative damage to cell membranes; protein carbonyls (PCs) show irreversible oxidative changes to proteins; and advanced oxidation protein products (AOPPs), which are associated with chronic inflammation and endothelial dysfunction [6]. Elevated concentrations of these biomarkers have been consistently related with both microvascular and macrovascular problems of diabetes, indicating that they have the ability to predict unfavorable cardiovascular outcomes [7].

The human body also has enzymatic antioxidant mechanisms that protect against oxidative assaults. Superoxide dismutase (SOD) transforms superoxide radicals to hydrogen peroxide, which is then detoxified by catalase (CAT) and glutathione peroxidase. These enzymes work together to maintain redox equilibrium. In T2DM, however, their activities are often reduced, resulting in decreased antioxidant defense, loss of redox equilibrium, and an increased vulnerability to vascular damage and cardiovascular events [8,9].

Although traditional cardiovascular risk variables including hypertension, dyslipidemia, and smoking remain important components of risk assessment, they may not entirely explain the remaining cardiovascular load in T2DM patients [10]. As a result, oxidative stress markers and antioxidant enzyme activity have emerged as intriguing additional predictors of cardiovascular risk. Integrating these factors into current clinical models may enhance risk prediction accuracy, enable more customized therapy, and allow for early preventative actions. This technique is particularly useful in low-resource countries, such as South Asia, where diabetes is prevalent and cost-effective risk stratification tools are urgently required [11].

Despite rising understanding of the role of oxidative stress in diabetes complications, few study have looked at the combined predictive usefulness of oxidative stress indicators and antioxidant enzyme activity in South Asian populations. Given the region's unique cultural, nutritional, and lifestyle features, such study is crucial for determining therapeutic value [12].

The present study was thus aimed to examine the connection between cardiovascular risk, as defined by the Framingham Risk Score, and blood levels of oxidative stress biomarkers (MDA, PCs, AOPPs) as well as antioxidant enzyme activity (SOD, CAT, GPx) in patients with T2DM. We predicted that greater oxidative stress and decreased antioxidant enzyme activity would be independently linked with increased cardiovascular risk in this cohort [13].

MATERIALS AND METHODS

This observational cross-sectional study was carried out from March 2023 to January 2025 at three tertiary care facilities in Pakistan. The study aimed to determine the relationship between cardiovascular risk, the antioxidant enzyme activity, and the biochemical indicators of oxidative stress in individuals with type 2 diabetes (T2DM). Ethical approval was given by the institutional review boards of all the involved institutions and all patients gave written informed consent before being included.

The criteria of the American Diabetes Association 2023 were used to recruit 120 persons with T2DM sequentially. Any participant aged between 35 and 70 years with a minimum period of illness of five years was eligible enough to guarantee inclusion of participants who have established chronic diabetes. The exclusion criteria in order to eliminate the potential confounding factors entailed the intake of long term antioxidant supplements, corticosteroids, recent acute infection, operation, myocardial infarction or stroke in the last six months, and end-stage chronic kidney disease, hepatic failure, autoimmune diseases, cancer, and other forms of diabetes (type 1 and gestational).

The following factors were reported: age, sex, body mass index (BMI), waist to hip ratio, smoking status,

length of diabetes, history of hypertension, medication usage, and lipid-lowering therapy. Following a five-minute break, a calibrated sphygmomanometer was used to take two readings of blood pressure while seated, and the average of the two readings was then analyzed. The Framingham Risk Score, which takes into account factors including age, gender, blood pressure, smoking, total cholesterol, and high-density lipoprotein (HDL) cholesterol, was used to assess cardiovascular risk. Based on the predicted scores, participants were categorized as either high risk or low-to-moderate risk.

Aseptic blood sample collection was done after a minimum 10-hour overnight fast. About 10 milliliters of venous blood were extracted, and they were centrifuged for 15 minutes at 3000 rpm. After being separated, the serum was stored at -80 °C until it was processed further. The thiobarbituric acid reactive chemicals test was used to measure the amounts of malondialdehyde (MDA), which were then expressed in nmol/mL. Following derivatization with dinitrophenylhydrazine, protein carbonyls (PCs) were quantified using spectrophotometry. Using a spectrophotometric method based on chloramine-T, advanced oxidation protein products (AOPPs) were measured and expressed in μmol/L. Antioxidant enzyme activity was measured using standardized biochemical assays: glutathione peroxidase (GPx) activity was measured by monitoring NADPH oxidation in the presence of glutathione and glutathione reductase, catalase (CAT) activity was measured by the rate at which hydrogen peroxide decomposed at 240 nm, and superoxide dismutase (SOD) activity was measured by inhibiting pyrogallol auto-oxidation. Standard units were used to quantify the activity of every enzyme. The lipid profile (total cholesterol, LDL, HDL, and triglycerides) was estimated using enzymatic colorimetric assays, the glycated hemoglobin (HbA1c) was measured using high-performance liquid chromatography, and the high-sensitivity C-reactive protein (hs-CRP) was measured as a measure of systemic inflammation.

Internal quality control protocols were strictly adhered to in order to reduce intra- and inter-assay variation to less than 5%, and all laboratory studies were carried out in triplicate to ensure repeatability. Laboratory staff were blinded to the cardiovascular risk categories of the patients in order to avoid observer bias. Based on previously reported differences in oxidative stress indicators between diabetic patients with and without cardiovascular issues, the sample size was determined using a priori power analysis. According to this calculation, 104 individuals would be required to achieve 80% statistical power at a significance level of 0.05 and an effect size of 0.5. The final sample size was expanded to 120 in order to account for any missing data and withdrawals.

SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Whereas categorical variables were presented as frequencies and percentages, continuous data were presented as mean ± SD. The data's normality was assessed using the Shapiro-Wilk test. The student's t-test was used to data that was regularly distributed, while the Mann-Whitney U test was applied to variables that were skewed. One-way ANOVA was used when comparing more than two groups. To look at relationships between category variables, the chi-square test was used. The associations between antioxidant enzyme activity, oxidative stress biomarkers, and cardiovascular risk scores were examined using Pearson's correlation coefficient. Multivariate logistic regression was used to find independent predictors of high cardiovascular risk after controlling for pertinent confounders such age, BMI, HbA1c, and lipid profile. Statistical significance was defined as a p-value of less than 0.05.

RESULTS

Among the 120 individuals with type 2 diabetes mellitus who were enrolled, 68 participants (56.7%) were classified as having low-to-moderate cardiovascular risk, while 52 (43.3%) were identified as belonging to the high-risk category, based on the Framingham Risk Score. The average age of the study population was 56.2 ± 8.3 years. In terms of sex distribution, males accounted for 64 cases (53.3%) and females for 56 (46.7%). Notably, men were disproportionately represented in the high-risk group, with 61.5% of them falling into this category compared with 38.5% of women. Conversely, women were more likely to appear in the low-to-moderate risk category (52.9% vs. 47.1%). This pattern suggests a gender-based disparity in cardiovascular risk among diabetic patients, aligning with established epidemiological trends that men typically develop cardiovascular complications earlier, whereas women experience a rapid increase in risk following menopause (Table 1).

Biochemical evaluation revealed that patients categorized as high risk had significantly poorer glycemic control compared with those in the low-to-moderate risk group. The average HbA1c in this category was 8.7 ± 1.2% ($p < 0.001$), indicating suboptimal metabolic regulation. Lipid disturbances were also more frequent and severe among high-risk individuals, with this group demonstrating higher levels of total cholesterol, LDL cholesterol, and triglycerides, alongside a reduction in HDL cholesterol. These alterations suggest that patients with elevated cardiovascular risk profiles continue to carry a heavier burden of conventional metabolic abnormalities despite ongoing therapy.

Assessment of oxidative stress biomarkers showed a distinct and statistically significant elevation in the high-risk group. Mean serum malondialdehyde (MDA) levels were almost twofold higher (5.4 ± 1.1 vs. 3.2 ± 0.7 nmol/mL; $p < 0.001$), indicating enhanced lipid peroxidation. Protein carbonyls (PCs), markers of irreversible oxidative modification of proteins, were also

increased (2.6 ± 0.5 vs. 1.8 ± 0.4 nmol/mg; p = 0.002). Similarly, advanced oxidation protein products (AOPPs), reflecting persistent oxidative and inflammatory processes, were markedly elevated in high-risk patients (92.1 ± 15.6 vs. 68.4 ± 12.3 µmol/L; p < 0.001). These findings highlight that individuals with higher predicted cardiovascular risk exhibit substantially greater oxidative burden compared with those at lower risk (Table 2).

In line with the elevated oxidative burden, activities of key antioxidant enzymes were found to be markedly reduced in patients at higher cardiovascular risk. The mean superoxide dismutase (SOD) level in the high-risk group was 5.1 ± 1.0 U/mL, significantly lower than the 7.2 ± 1.3 U/mL observed in the low-to-moderate risk group (p < 0.001). Catalase (CAT) activity also declined in the high-risk category (33.8 ± 5.9 vs. 42.5 ± 6.2 kU/L; p < 0.01). Similarly, glutathione peroxidase (GPx) activity was reduced to 49.5 ± 7.2 U/mL compared with 62.7 ± 8.4 U/mL in lower-risk individuals (p < 0.01). These consistent reductions across all three enzymes indicate that weakened endogenous antioxidant defenses contribute to disruption of redox balance, thereby facilitating oxidative damage and vascular dysfunction in T2DM patients with increased cardiovascular risk (Table 3).

Table-1: Gender distribution among study participants according to cardiovascular risk

Gender	Low/Moderate Risk (n = 68)	High Risk (n = 52)	Total (n = 120)
Male	32 (47.1%)	32 (61.5%)	64 (53.3%)
Female	36 (52.9%)	20 (38.5%)	56 (46.7%)

Table-2: Comparison of oxidative stress biomarkers between cardiovascular risk groups

Biomarker	Low/Moderate Risk (n = 68)	High Risk (n = 52)	p-value
Malondialdehyde (nmol/mL)	3.2 ± 0.7	5.4 ± 1.1	<0.001
Protein Carbonyl (nmol/mg protein)	1.8 ± 0.4	2.6 ± 0.5	0.002
AOPPs (µmol/L)	68.4 ± 12.3	92.1 ± 15.6	<0.001

Table-3: Comparison of antioxidant enzyme activities between cardiovascular risk groups

Enzyme	Low/Moderate Risk (n = 68)	High Risk (n = 52)	p-value
Superoxide Dismutase (U/mL)	7.2 ± 1.3	5.1 ± 1.0	<0.001
Catalase (kU/L)	42.5 ± 6.2	33.8 ± 5.9	<0.01
Glutathione Peroxidase (U/mL)	62.7 ± 8.4	49.5 ± 7.2	<0.01

Multivariate logistic regression analysis confirmed that disturbances in oxidative balance independently predicted cardiovascular risk within the study population. Patients with elevated malondialdehyde (MDA) levels had nearly a threefold greater probability of being classified as high risk (OR 2.9, 95% CI: 1.8–4.5; p < 0.001). Likewise, reduced superoxide dismutase (SOD) activity was associated with a 2.3-fold increase in the likelihood of belonging to the high-risk category (OR 2.3, 95% CI: 1.4–3.9; p = 0.002). Such associations could be observed despite the traditional risk factors, such as age, body mass index, HbA1c, and lipid profile parameters.

Collectively, the results indicate that patients with T2DM that belong to the high cardiovascular risk group exhibits a dual profile of defects, i. e. higher levels of oxidative stress indicators and reduced antioxidant capabilities. The extra finding of gender variations highlights the effects of sex-specific biological factors on the risk stratification of cardiovascular diseases in diabetes. Generally speaking, all these findings give a good biological foundation and clinical rationale regarding the inclusion of oxidative stress profiling into the cardiovascular risk assessment models of patients with T2DM.

DISCUSSION

This study revealed that there was a very close association of oxidative stress, antioxidant enzyme activity, and the cardiovascular risk among individuals with type 2 diabetes (T2DM) [10]. A high Framingham Risk Score was accompanied by a significant increase in the levels of malondialdehyde (MDA), protein carbonyls (PC), and advanced oxidation protein products (AOPPs) and reduced activity of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) levels [11].

Notably, regression analysis indicated that increased MDA and reduced SOD activity had significant predictive values of cardiovascular risk on condition of other established variables of metabolic risks. These data support the theory that oxidative stress is a major contributor to the development of cardiovascular problems in T2DM [12,13]. Persistent hyperglycemia increases reactive oxygen species (ROS) generation via routes such as mitochondrial dysfunction, glucose autoxidation, and NADPH oxidase activity. The buildup of ROS causes lipid peroxidation, protein oxidation, and DNA damage, all of which contribute to endothelial dysfunction, vascular inflammation, and atherosclerosis development. In this group, high-risk patients had significantly higher MDA levels, indicating continuous lipid peroxidation, but greater PCs and AOPPs indicated irreversible oxidative changes in circulating proteins, both of which are associated with vascular stiffness and plaque instability [14,15].

The observed decline in antioxidant enzyme activity emphasizes the imbalance between ROS generation and defense mechanisms. Under normal circumstances, SOD

converts superoxide radicals to hydrogen peroxide, which is subsequently neutralized by CAT and GPx [16]. Decreased activity of these enzymes, as reported in high-risk individuals, reduces the body's redox buffering ability, prolongs oxidative exposure, and increases vascular damage. Previous investigations found similar findings, identifying reduced antioxidant enzyme activity as a critical stage in the development from metabolic disruption to overt cardiovascular illness [17].

The discovery of MDA and SOD as independent indicators of cardiovascular risk highlights their potential as therapeutically useful biomarkers. Although extensively used, classic risk prediction models like the Framingham score rely heavily on age, lipid profile, smoking, and blood pressure [18]. These models, however, do not adequately represent the residual risk reported in T2DM patients, especially in South Asian communities where early onset of diabetes, specific lifestyle variables, and genetic susceptibility all contribute to a heightened cardiovascular burden. The addition of oxidative stress markers to standard models should improve risk categorization and allow for earlier discovery of sensitive individuals [19].

Sex-based disparities discovered in this study provide more context. Men were more commonly represented in the high-risk group, which is consistent with worldwide data that diabetes men have cardiovascular events earlier than women [1,20]. Nonetheless, following menopause, women lose estrogen-mediated vascular protection, putting them at equal or even greater risk than males. These results emphasize the need of incorporating gender-specific considerations into preventative measures, especially in settings where oxidative stress may exacerbate sex-related risk disparities.

The clinical implications of these findings are significant [17,21]. Oxidative stress indicators and antioxidant enzyme activity might be used as low-cost additional techniques to identify people at high risk of cardiovascular events. Furthermore, therapies to reduce oxidative stress have therapeutic potential [22]. Weight control, exercise, and antioxidant-rich foods have all been found to increase antioxidant defenses. Pharmacological medications such as metformin, statins, and ACE inhibitors, as well as newer medicines like as SGLT2 inhibitors and GLP-1 receptor agonists, have antioxidant benefits in addition to their main mechanisms. Although antioxidant supplements like vitamin E, coenzyme Q10, and polyphenols have had mixed results in clinical trials, bigger, more organized study are required to assess their real therapeutic usefulness. These results are particularly important for South Asia, where both diabetes and cardiovascular disease are on the rise. In resource-constrained settings, low-cost oxidative stress tests might be a useful tool for early risk identification, leading prompt actions to prevent cardiovascular morbidity and death [23,24].

This study has limitations. Its cross-sectional design limits the capacity to infer causation, and longterm investigations are needed to determine if oxidative stress indicators predict incident cardiovascular events. The sample size, although statistically significant, was modest and restricted to three tertiary institutions, thereby decreasing generalizability. Furthermore, non-enzymatic antioxidants such as glutathione, uric acid, and vitamins C and E were not tested, which may have given a more comprehensive picture of antioxidant status. Despite these limitations, the data provide compelling evidence that oxidative stress profiling may improve cardiovascular risk assessment in T2DM patients [25].

CONCLUSION

The findings of this study indicate that patients with type 2 diabetes mellitus at higher cardiovascular risk present with a distinct imbalance, characterized by elevated oxidative stress markers and reduced antioxidant enzyme activity. Among these, malondialdehyde (MDA) and superoxide dismutase (SOD) were identified as independent predictors, underscoring their importance beyond conventional risk factors. Incorporating oxidative stress profiling into cardiovascular risk evaluation may enhance the accuracy of risk stratification, especially in regions with a heavy disease burden such as South Asia. Early identification of high-risk individuals and interventions directed at restoring redox balance could provide an effective strategy to lower cardiovascular morbidity and mortality in this population.

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Authors' contributions:

IA: Conceptualization, Data Collection.
HK: Methodology, Literature Review.
NA: Data Analysis, Drafting.
AD: Laboratory Work, Validation.
JA: Clinical Supervision, Revision.
M: Review, Editing, Proofreading.

Data Availability Statement: The data used in this study are available upon reasonable request from the corresponding author, subject to ethical and institutional guidelines.

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