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Research Article

Integrated Evaluation of Serum Oxidative Stress Markers and Histopathological Grading in Predicting Early Organ Damage in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a persistent metabolic illness linked with an advancement of microvascular and macrovascular issues. Oxidative stress has a critical role in the pathogenesis of diabetic organ injury, but its combination with histopathological grading to predict early remains underdeveloped.

Objective: To assess the relationship between serum oxidative stress markers and histopathological grading in accurately forecasting early organ damage in T2DM patients.

Methods: This cross-sectional clinical study was conducted from June 2024 to June 2025 at Gujranwala Medical College, Gujranwala, Pakistan, and Khawaja Muhammad Safdar Medical College, Sialkot, Pakistan. One hundred and twenty (120) T2DM patients (35–65 years old) were recruited by non-probability consecutive sampling. The ELISA was used to measure serum levels of malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH). The tissue biopsies were histopathologically graded using standard criteria (Grade I–III). The statistical analysis involved the use of SPSS version 26, with $p < 0.05$ being significant.

Results: The average age of the participants was 53.1 ± 9.2 years, and 56.7% were males. The mean HbA1c level was 9.2 ± 1.5%. Elevated MDA levels (4.9 ± 1.3 nmol/mL) and reduced antioxidant markers SOD (2.0 ± 0.7 U/mL) and GSH (3.1 ± 1.0 µmol/L) were observed. The histopathological changes were 31.7% Grade I, 43.3% Grade II, and 25.0% Grade III. The increase in MDA (3.3 ± 0.9 to 6.1 ± 1.4 nmol/mL) and the corresponding decrease in SOD and GSH levels ($p < 0.001$) corresponded with increasing grades. There was a high positive correlation between MDA and tissue damage ($r = +0.71$) and negative correlations for SOD ($r = −0.57$) and GSH ($r = −0.62$). Early organ damage in 61.7% of patients was mostly the kidneys (38.3%) and the liver (23.3%).

Conclusion: Histopathological severity is closely linked with serum oxidative stress markers, which can be used as quality early predictors of organ damage in T2DM. Biochemical analysis combined with histological analysis is a promising method of early diagnosis and risk stratification.

Keywords: Type 2 Diabetes Mellitus, Oxidative Stress, Malondialdehyde, Superoxide Dismutase, Glutathione, Histopathological Grading, Organ Damage.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is an emerging worldwide health issue, with chronic hyperglycemia caused by an interplay of insulin resistance and insulin secretion disruption[1]. The multiple chronic complications associated with the disease include nephropathy, hepatopathy, neuropathy, and cardiovascular disorders that result in high morbidity and mortality. The rate at which T2DM is rising in developing countries such as Pakistan is alarming, partly due to urbanization, sedentary lifestyles, and dietary habits; hence, there is a need to identify the

damage to the organs at early stages before it becomes a runaway phenomenon[2].

Oxidative stress is one of the key processes in the pathogenesis of diabetic complications, and it can be defined as an imbalance between the generation of reactive oxygen species (ROS) and the inefficiency of the antioxidant defense system to resist them[3]. The sustained hyperglycemia of T2DM promotes the excessive production of ROS through a number of biochemical pathways that include glucose autoxidation, activation of the polyol pathway, activation of protein kinase C, and formation of advanced glycation end products (AGEs). Results of these processes are lipid peroxidation, alteration of proteins, and damage to DNA, and ultimately dysfunction of cells and structural tissue damage[4].

Malondialdehyde (MDA), being one of the many biomarkers of oxidative stress, is considered an excellent indicator of lipid peroxidation and oxidative damage[5]. On the other hand, endogenous antioxidant systems such as superoxide dismutase (SOD) and glutathione (GSH) are of great protective importance because of their ability to inhibit the free radicals and maintain redox homeostasis. Changes in these markers indicate the degree of oxidative imbalance and are more and more related to the intensity of diabetic complications. But biochemical markers do not necessarily give a complete picture of the degree of structural damage to organs[6].

The gold standard of measuring changes at the tissue level, which is a direct indicator of cellular damage, inflammation, fibrosis, and vascular changes, is the histopathological assessment[7]. Histopathological grading can be used to objectively categorize the severity and progression of a disease. Although the role of oxidative stress markers and histopathological evaluation has an individual significance, there is a relative dearth of study that has combined both methods to assess the early organ damage in T2DM patients[8].

Subclinical organ involvement is an early onset that is highly essential in preventing the further development of advanced complications. Therefore, a combined assessment of biochemical oxidative stress markers and histopathological grading may offer a more sensitive and comprehensive approach for early diagnosis and risk stratification in T2DM[9].

The current study aims to show the correlation between serum oxidative stress biomarkers MDA, SOD, and GSH with histopathological grading of tissue damage, as well as the combined effect of these biomarkers in the prediction of early organ damage in patients with type 2 diabetes mellitus[10].

MATERIALS AND METHODS

This cross-sectional clinical study was conducted over a period of one year, from June 2024 to June 2025, at the Department of Biochemistry and affiliated clinical units of Gujranwala Medical College, Gujranwala, Pakistan, and Khawaja Muhammad Safdar Medical College, Sialkot, Pakistan. The study aimed to assess the combined value of serum oxidative stress markers and histopathological grading to predict early organ damage in patients with type 2 diabetes mellitus.

The study used non-probability sampling to enroll 120 patients who had been previously diagnosed with type 2 diabetes mellitus. Participants were adult patients aged 35-65 years of either sex with a known positive diagnosis of T2DM at least one year prior. Outpatient and inpatient medical units of the participating institutions were used to recruit their patients. Diagnosis of T2DM was determined by medical records, fasting blood glucose, glycated hemoglobin, and history of antidiabetic treatment. Patients who had acute infectious diseases, chronic inflammatory diseases, malignancy, chronic liver disease not associated with diabetes, end-stage renal disease, autoimmune diseases, pregnant, or antioxidant supplementation were excluded to exclude confounding effects on oxidative stress status and tissue pathology.

After the enrollment of the participants, a detailed clinical history was obtained about them, including age, sex, diabetes history, treatment history, comorbidities, and symptoms that could potentially signify early organ involvement. A structured proforma was used to record demographic and clinical data. General physical examination and relevant systemic examination were done on all patients. The biochemical examination involved the enrollment of baseline laboratory results, such as fasting blood glucose and a glycated hemoglobin (HbA1c) level.

For oxidative stress analysis, 5 mL of venous blood was collected under aseptic conditions from each participant. Blood samples were centrifuged, and after separating serum, it was stored at the necessary temperature till analysis. Malondialdehyde (MDA), a lipid peroxidation stress marker; superoxide dismutase (SOD), an enzymatic antioxidant stress marker; and reduced glutathione (GSH),

a major non-enzymatic antioxidant stress marker, were the serum oxidative stress markers measured in the study. Enzyme-linked immunosorbent assay (ELISA) kits were used to analyze these parameters as per the recommendations of the manufacturer. The entire assays were performed under a set of research laboratory conditions of the respective institutions under standardized conditions to ensure reliability and reproducibility of results.

The histopathological evaluation was conducted in patients in whom tissue sampling was clinically dictated based on the supposed early organ involvement, especially tissue alterations in renal or hepatic tissue, in diabetic complications. Specimen Tissues: Tissue specimens were collected by the mentioned biopsies and processed in the pathology labs of the participating institutions. The samples were fixed in formalin, embedded in paraffin, and then sectioned and stained using hematoxylin and eosin (H&E) to examine them under the microscope. Grading was done using histopathological methods by a group of experienced histopathologists who were not aware of the biochemical results. Tissue alterations were classified as Grade I, Grade II, and Grade III based on the extent of cellular damage, inflammatory response, degeneration, and initial fibrosis. Grade I was mild tissue change, Grade II moderate tissue damage, and Grade III conspicuous or severe early tissue damage.

Early organ damage was measured based on biochemical, clinical, and histopathological results. Renal involvement was determined when there were diabetic nephropathic alterations, and hepatic involvement was examined by histological evidence of steatosis, inflammation, or early fibrosis in clinically suspected cases. The correlation between the oxidative stress markers and those of histopathology grades was then examined with an aim of establishing their predictive value in early organ damage in diabetes.

The data gathered were analyzed and input into SPSS version 26.0. Quantitative variables such as age, duration of diabetes, HbA1c, MDA, SOD, and GSH levels were expressed as mean ± standard deviation. The data on sex distribution, histopathological grades, and the frequency of organ involvement were reported as frequencies and percentages as qualitative variables. One-way analysis of variance (ANOVA) was used to compare the levels of oxidative stress markers at different histopathological grades. The chi-square test was used to determine the relationship between categorical variables. Pearson correlation analysis was used to determine the relationship between serum oxidative stress markers and histopathological severity. A p-value below 0.05 was considered statistically significant.

The study was ethically approved by the Institutional Ethical Review Committees before the data collection started. This study was done under the principles of the Declaration of Helsinki. All participants were informed and gave written consent to participate in the study, and patient information was confidentially maintained during the entire research process.

RESULTS

A total of 120 patients with type 2 diabetes mellitus (T2DM) were included in the present study, providing a comprehensive dataset for evaluating the relationship between oxidative stress markers and histopathological grading in predicting early organ damage. The average age of the sample population was 53.1 ± 9.2 years and represented a rather middle-aged to elderly group, as a higher number of males (n=68, 56.7%) were observed than females (n=52, 43.3%). The mean length of diabetes was 9.16 ± 3.8 years, and this implies that the patients were mostly long-term sufferers of the disease, and this factor is associated with an elevated tendency to develop microvascular and macrovascular complications. Also, the average value of glycated hemoglobin (HbA1c) was 9.2 ± 1.5, which indicates ineffective glycemic regulation in most of the participants and leads to further oxidative stress and subsequent tissue damage. Table 1 summarizes these baseline demographic and clinical characteristics and indicates that the study population is a high-risk diabetic group that is likely to damage its organs early.

Table 1: Baseline Demographic and Clinical Characteristics of Study Population

Variable	Value
Total patients (n)	120
Mean age (years)	53.1 ± 9.2
Male	68 (56.7%)
Female	52 (43.3%)
Duration of diabetes (years)	9.1 ± 3.8

HbA1c (%)	9.2 ± 1.5

Biochemical analysis of the oxidative stress markers showed that there was a considerable disequilibrium between pro-oxidant and antioxidant activity in the T2DM patients. It was revealed that the mean serum level of malondialdehyde (MDA), which is a well-established lipid peroxidation biomarker, was significantly high (4.9 ± 1.3 nmol/mL), suggesting greater oxidative damage on a cellular level. The defense mechanisms of antioxidant defense, conversely, were also highly affected as indicated by reduced levels of superoxide dismutase (SOD) (2.0 ± 0.7 U/mL) and glutathione (GSH) (3.1 ± 1.0 µmol/L). The results presented in Table 2 indicate that the patients with T2DM experience a considerable amount of oxidative load, which can trigger the tissue injury onset and evolution even before the emergence of the obvious clinical complications. Such an imbalance between the elevated levels of oxidants and the low levels of antioxidant stores underscores the pathophysiology of oxidative stress in the destruction of organs in diabetic patients.

Table 2: Serum Oxidative Stress Markers in Study Population

Marker	Mean ± SD
MDA (nmol/mL)	4.9 ± 1.3
SOD (U/mL)	2.0 ± 0.7
GSH (µmol/L)	3.1 ± 1.0

The histopathological analysis of the tissue samples received as a result of clinically referenced biopsies showed that there were different levels of structural and cellular changes in the participants of the study. The histopathological grade distribution revealed that 38 patients (31.7%) had Grade I changes (that is, mild cellular changes and early degenerative changes), and 52 patients (43.3%) had Grade II changes (that is, moderate structural damage and more pronounced inflammatory and degenerative changes). Interestingly, 30 patients (25.0%) had Grade III changes, which is a severe early tissue injury, with severe architectural distortion and early fibrotic changes. The summary of these findings in Table 3 shows that a significant percentage of patients had developed moderate or severe histopathological damage, even though they are in the initial stages of organ involvement that can be clinically detected. This highlights the tissue-level silent development of diabetic complications.

Table 3: Distribution of Histopathological Grades

Grade	Frequency (n)	Percentage (%)
Grade I (Mild)	38	31.7%
Grade II (Moderate)	52	43.3%
Grade III (Severe)	30	25.0%

Comparative analysis of oxidative stress markers in different histopathological grades showed that there was a very significant and progressive correlation between oxidative imbalance and tissue damage severity. MDA levels in serum showed a significant progressive elevation with the worsening histopathological grade, with a rise in serum MDA levels of 3.3 ± 0.9 nmol/mL in Grade I, 4.8 ± 1.1 nmol/mL in Grade II and 6.1 ± 1.4 nmol/mL in Grade III, reflecting growing lipid perox On the other hand, there was a significant and steady decrease in antioxidant markers with increasing damage grades. The mean SOD levels decreased from 2.9 ± 0.6 U/mL in Grade I to 2.1 ± 0.5 U/mL in Grade II, and further to 1.4 ± 0.4 U/mL in Grade III, while GSH levels declined from 4.6 ± 0.8 µmol/L to 3.2 ± 0.7 µmol/L and 2.2 ± 0.6 µmol/L across the respective grades. All these results, as shown in Table 4, were statistically significant ($p < 0.001$) in that the trend of increasing oxidative stress and decreasing antioxidant capacity is strongly related to aggravation of histopathological damage. The trend is a clear indication that oxidative stress is a major contributor to tissue damage in T2DM.

Table 4: Comparison of Oxidative Stress Markers Across Histopathological Grades

Marker	Grade I	Grade II	Grade III	p-value

MDA (nmol/mL)	3.3 ± 0.9	4.8 ± 1.1	6.1 ± 1.4	<0.001
SOD (U/mL)	2.9 ± 0.6	2.1 ± 0.5	1.4 ± 0.4	<0.001
GSH (µmol/L)	4.6 ± 0.8	3.2 ± 0.7	2.2 ± 0.6	<0.001

These observations were further supported by further statistical analysis based on Pearson correlation analysis, which revealed that the level of MDA and histopathological severity had a strong positive correlation ($r = +0.71$, $p < 0.001$), and high levels of oxidative stress are directly correlated with more severe tissue damage. Conversely, SOD ($r = -0.57$) and GSH ($r = -0.62$) exhibited strong negative relationships with the histopathological grading, indicating that a lower level of antioxidant defenses is strongly associated with the development of tissue injury. Table 5 below illustrates these correlations, which elucidate the dual role of increased oxidative stress and reduced antioxidant capacity in causing organ damage in T2DM patients.

Table 5: Correlation Between Oxidative Stress Markers and Histopathological Severity

Marker	Correlation Coefficient (r)	p-value
MDA	+0.71	<0.001
SOD	−0.57	<0.001
GSH	−0.62	<0.001

Early organ involvement was assessed by gathering combined clinical, biochemical, and histopathological evidence of early organ damage that was observed in 74 patients (61.7%). The most common of these was renal involvement, which was found in 46 patients (38.3%), then hepatic involvement was found in 28 patients (23.3%), and finally, no significant organ involvement was detected in 46 patients (38.3%). These results, which can be summarized in Table 6, suggest that kidneys are specifically susceptible to early oxidative damage in T2DM, before the liver, as a systemic effect of chronic hyperglycemia and oxidative stress. The fact that subclinical organ damage is extremely common also highlights the need to employ early detection strategies.

Table 6: Frequency of Early Organ Damage

Organ Involvement	Frequency (n)	Percentage (%)
Renal involvement	46	38.3%
Hepatic involvement	28	23.3%
No significant involvement	46	38.3%

Overall, the results of this study demonstrate a clear, progressive, and statistically significant relationship between oxidative stress markers and histopathological grading of tissue damage. The results are highly suggestive of the idea that enhanced oxidative stress, as indicated by higher levels of MDA as well as loss of major antioxidant protective mechanisms like SOD and GSH, is a critical factor in the early onset of organ damage in patients with type 2 diabetes mellitus. A combination of biochemical and histopathological analysis offers a solid and clinically significant method for early detection and risk classification of diabetic complications.

DISCUSSION

The present study provides a comprehensive evaluation of the relationship between oxidative stress markers and histopathological grading in predicting early organ damage in patients with type 2 diabetes mellitus (T2DM)[8]. The results clearly show that oxidative stress is central and progressively involved in the pathogenesis of tissue injury, even in the initial phases of diabetic complications. The sampling was made up of mostly middle-aged people having long-lasting diabetes and poor glycemic control as indicated by high levels of HbA1c. This has clinical implications because chronic hyperglycemia is an established source of oxidative stress by using a variety of metabolites to ultimately cause cells to dysfunction and organs to be damaged[9].

The key findings of this study included the high levels of malondialdehyde (MDA) that were observed in patients with higher histopathological grades. MDA is an end-product of lipid peroxidation, and is a good predictor of oxidative damage to cell membranes[10]. The progressive increase in the level of MDA between Grade I and Grade III tissue damage suggests that lipid peroxidation

rises with structural damage. This finding is in line with past reports that have found elevated MDA concentrations as a signature of oxidative stress among diabetic patients and their high correlations with microvascular complications like nephropathy and hepatopathy. Another supporting factor of MDA as a potential early biomarker of tissue damage is the positive correlation that is reported between MDA and histopathological severity ($r = +0.71$)[11].

Conversely, the study has shown that antioxidant defense systems, especially superoxide dismutase (SOD) and glutathione (GSH), decreased significantly with the increasing severity of histopathological damage[12]. SOD is an important enzyme antioxidant that splits the superoxide radical into hydrogen peroxide, and GSH is an important intracellular antioxidant that reacts with the free radicals to protect against oxidative damage as well as maintain redox balance. These antioxidant markers have been observed to reduce, which is an indicator of an overloaded defence in the case of chronic oxidative stress. The negative correlation of SOD ($r = -0.57$) and GSH ($r = -0.62$) with histopathological grading highlights the protective impact and demonstrates that the depletion of antioxidant reserves can be a key determinant in tissue damage[13,14].

The combination of biochemical indicators and histopathological evaluation is also an interesting aspect of the study, as it provides first-hand evidence of structural tissue damage[15]. Whereas biochemical signals indicate the presence of functional and metabolic alterations, histopathology determines the presence and extent of cellular injury, inflammation, and early fibrosis. The general histopathology changes of Grade II prevalence (43.3% in this study) suggest that moderate tissue damage is already present in a significant percentage of the patients, before the clinical manifestations of organ dysfunction become noticeable. The observation emphasizes the insidiousness of the diabetic complications and the importance of their early diagnosis and prevention steps[16].

The study has also demonstrated that early organ involvement was also noted in 61.7% of the patients whose kidney was the most affected organ at that time, followed by the liver[17]. This contributes to the fact that the renal tissue is known to be extremely vulnerable to oxidative damage due to its high metabolic index and high density of microvascular network. Oxidative stress caused by hyperglycemia results in glomerular damage, mesangial proliferation, and premature nephropathic alterations, which could develop into chronic kidney disease when not treated in the early stages. Similarly, the hepatic alterations, which are steatosis, inflammation, and early fibrosis, depict the dysmetabolism of T2DM on a systemic level[18].

The combination of the oxidative stress markers with the histopathological grading of the study gives a more sensitive and comprehensive method of early organ damage detection. This combined method provides the possibility to detect subclinical changes, unlike the traditional methods of diagnosis, which use late clinical signs, thus enabling early intervention. The results indicate that the regular testing of the oxidative stress indicators, especially the MDA, SOD, and GSH, could be an important addition to the traditional diagnostic measures in the treatment of T2DM[19,20].

This study has limitations despite its strengths. The cross-sectional design limits the ability to establish causal relationships between oxidative stress and tissue damage. Additionally, the study was conducted in a limited number of centers with a relatively moderate sample size, which may affect the generalizability of the findings. Moreover, histopathological evaluation was performed when clinical signs appeared, which may introduce a selection bias. These findings should be confirmed by future longitudinal studies with bigger sample sizes and multi-centric participation to examine the prognostic relevance of oxidative stress markers across the long term[15-20].

CONCLUSION

The findings of this study demonstrate that serum oxidative stress markers, particularly malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH), are significantly associated with histopathological grading of tissue damage in patients with type 2 diabetes mellitus. Both high oxidative stresses, evidenced by high levels of MDA and loss of antioxidant defenses, are closely associated with the degree of early organ damage. Integration of biochemical and histopathological analysis is a potent and clinically important strategy for early detection and prediction of organ damage in T2DM. This form of an integrated approach can help to boost the stratification of risks, preinform initial therapeutic actions, and ultimately reduce the cost of long-term diabetic complications. To identify the high-risk patients before irreversible

damage to organs, regular screening of the indicators of oxidative stress may prove to be a useful tool in clinical practice. Further massive and longitudinal studies are warranted to come up with standardized diagnostic guidelines and to examine particular antioxidant-based therapies in the treatment of type 2 diabetes mellitus.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

F.S., S.A.R., and H.M.U. contributed to the study conception and design.
I.H. and H.S. were involved in data collection and laboratory analysis.
R.S. and H.M.U. contributed to statistical analysis and interpretation of results.
E.A.K. supervised the study and finalized the manuscript.
All authors read and approved the final manuscript.

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