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Evaluating diabetic nephropathy Severity by the 8-OHDG, AGEs and oxidative stress Biomarkers

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Abstract

Back ground

End-stage kidney disease (ESKD) is most commonly caused by diabetic kidney disease (DKD) in affluent nations, including the US. It is a microvascular complication that can arise in people with type 1 diabetes (T1DM) or type 2 diabetes (T2DM).Aims of the study: Understanding the connection between vitamin D and Cytokine levels in diabetic nephropathy patients.Result : The study's 90 participants (40 women and 50 men) showed a wide variety of ages, with most of them being between 45 and 82. The study compared the relationship between diabetic nephropathy and several kidney function parameters in males and females, showing differences in the levels 8-OHDG, AGEs and oxidative stress Biomarkers. The comparison of oxidative stress biomarker (MDA, 8OHDG, AOPP, HNE4 and AGE) between patient and control groups has been carried out.

Conclusions: It has been observed that the values of kidney efficiency parameters are affected in diabetic patients after a number of years, and as a result this leads to an increase in the values of these parameters, which ultimately leads to kidney damage or severe damage, which makes the people concerned need to undergo dialysis or even a kidney transplant, or in late cases it may lead to death.

Introduction:

Chronic hyperglycemia is a characteristic that is characteristic of diabetes mellitus, which is a metabolic state that does not go away with the passage of time. It is possible that deficiencies in insulin production, insulin action, or a combination of all of these characteristics are the ones that are responsible for this condition. Glucose levels in the blood may be regulated by the pancreas via the production of insulin, which is a hormone that is termed insulin. Insulin is a hormone. Insulin plays a significant part in promoting glucose's entrance into cells, which enables glucose to be utilised for the creation of energy. In the event that insulin production is inadequate or if its action is inhibited, it is possible for glucose to accumulate in the circulation over a period of time. The findings of (1).

Types of Diabetes Mellitus

A-Type 1 Diabetes (T1D)

1- Cause: Type 1 diabetes is primarily caused by an autoimmune reaction where the body's immune system attacks and destroys the insulin-producing beta cells in the pancreas. This destruction leads to little or no insulin production, necessitating external insulin administration (2).
2- Onset: This type of diabetes is typically diagnosed in children and young adults, although it can occur at any age. It is often identified through sudden symptoms such as extreme thirst, frequent urination, unexplained weight loss, and high levels of ketones in the urine.
3- Management: Management of T1D involves regular insulin therapy, which can be administered through injections or an insulin pump. Patients must frequently monitor their blood glucose levels, follow a balanced diet, and engage in regular physical activity to manage their blood sugar levels effectively. Additionally, continuous glucose monitoring (CGM) devices can help in maintaining optimal glucose control (2).

B- Type 2 Diabetes (T2D)

1- Cause: Type 2 diabetes is primarily caused by insulin resistance, a condition in which the body's cells do not respond properly to insulin. Over time, the pancreas may also produce less insulin. Risk factors include genetic predisposition, obesity, physical inactivity, poor diet, and increasing age (3).
2- Onset: T2D is most commonly diagnosed in adults over 45, but it is increasingly being seen in younger populations, including children, adolescents, and young adults, due to rising obesity rates. Symptoms develop gradually and may include increased thirst, frequent urination, hunger, fatigue, and blurred vision.
3- Management: Lifestyle modifications including eating a balanced diet, exercising often, and controlling weight are key components of T2D management. Medications are often required, starting with oral hypoglycemic agents like metformin. Other medications may include sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists. In some cases, insulin therapy may become necessary. Regular monitoring of blood glucose levels and HbA1c is essential for managing the disease (3).

C- Gestational Diabetes Mellitus (GDM)

1- Cause: Insulin resistance is a hallmark of gestational diabetes, which develops throughout pregnancy. Increased body weight and hormonal changes are two factors that contribute to this resistance.
2- Women who have a family history of diabetes, obesity, or prior GDM are more prone to experience it.
3- Onset: GDM is typically diagnosed during the second or third trimester of pregnancy through routine screening tests such as the oral glucose tolerance test (OGTT). Symptoms may be mild or absent, but some women may experience increased thirst and urination.
4- Management: Management of GDM involves dietary modifications, regular physical activity, and blood glucose monitoring. If lifestyle changes are insufficient, insulin therapy may be required to maintain blood glucose levels within target ranges. GDM usually resolves after delivery, but women who have had GDM are at higher risk of developing T2D later in life (4).

D- Other Specific Types

Maturity-Onset Diabetes of the Young (MODY): MODY represents a collection of monogenic disorders resulting from mutations in particular genes that influence insulin production. MODY is inherited in an autosomal dominant pattern, distinguishing it from T1D and T2D. Various forms of MODY exist, each linked to distinct genetic mutations. Diagnosis typically takes place during adolescence or early adulthood, with management strategies potentially involving lifestyle modifications and oral medications instead of insulin (5).

Secondary Diabetes: This type of diabetes develops due to a range of medical conditions or treatments that impair insulin secretion or its efficacy. Secondary diabetes may arise from a range of conditions, such as pancreatitis, cystic fibrosis, hemochromatosis, and hormonal disorders including Cushing's syndrome. Medications such as glucocorticoids, certain antipsychotics, and antiretrovirals may play a role in the development of diabetes. Effective management necessitates addressing the underlying condition and regulating blood glucose levels through suitable lifestyle modifications and medications as required (6).

The incidence of Type 2 diabetes is increasing among younger demographics, including children and adolescents, reflecting the escalating rates of obesity and sedentary habits. Diabetic nephropathy is a common and serious complication linked to type 2 diabetes, characterised by kidney damage resulting from prolonged high blood sugar levels. This condition is the leading cause of end-stage renal disease (ESRD) globally, significantly elevating the risk of cardiovascular disease and mortality. Approximately 20–40% of individuals with type 2 diabetes are affected by nephropathy, highlighting the global importance of this complication (7).

Pathophysiology of Diabetic Nephropathy

Diabetic nephropathy, also known as diabetic kidney disease, is a severe microvascular complication of diabetes and the leading cause of end-stage renal disease (ESRD) globally. Its pathophysiology is complex and involves multiple intertwined mechanisms, including hyperglycemia, oxidative stress, inflammation, hemodynamic abnormalities, and genetic factors (8). Chronic hyperglycemia is a key driver in the pathogenesis of diabetic nephropathy, leading to the accumulation of advanced glycation end products (AGEs). AGEs form through non-enzymatic reactions between glucose and proteins, lipids, or nucleic acids, which cause structural and functional changes in these molecules. The buildup of AGEs in renal tissues, particularly in glomerular and tubular

cells, triggers cellular dysfunction, abnormal tissue remodeling, and heightened inflammatory responses. The interaction of AGEs with their receptor, known as RAGE, on renal cells stimulates the production of pro-inflammatory cytokines and reactive oxygen species (ROS), further contributing to kidney damage (9). Oxidative stress plays a central role in diabetic nephropathy and results from an imbalance between ROS production and the body's antioxidant defenses. This imbalance leads to cellular injury, inflammation, and fibrosis within kidney tissue. Oxidative stress disrupts normal cellular functions and accelerates fibrosis by increasing the synthesis of extracellular matrix proteins, which accumulate in glomerular and tubulointerstitial compartments, resulting in tissue remodeling and loss of renal function (10). Additionally, inflammatory pathways are activated in response to hyperglycemia and oxidative stress, with the kidney producing chemokines and cytokines, such as TNF-alpha and IL-6, that recruit immune cells and induce sustained inflammation and fibrosis (11). Another major factor in diabetic nephropathy is dysregulation of the renin-angiotensin-aldosterone system (RAAS), a hormonal system crucial for blood pressure and fluid balance. Diabetes-induced RAAS activation leads to systemic and intrarenal hypertension, hyperfiltration, and glomerular hypertension, which accelerate kidney damage. This hyperfiltration increases pressure in the glomerular capillaries, resulting in structural alterations, increased permeability, and eventual proteinuria. Proteinuria itself further exacerbates kidney damage by causing tubular injury and inflammatory responses within the interstitial tissue (12). Fibrosis is a hallmark of diabetic nephropathy, characterized by an excessive accumulation of extracellular matrix proteins that replace healthy renal tissue. This fibrotic process is triggered by prolonged hyperglycemia, oxidative stress, and inflammation, ultimately leading to the replacement of functional renal tissue with fibrotic tissue. Fibrosis impairs renal function and progresses to kidney failure if not managed effectively. Moreover, proteinuria, a result of increased glomerular permeability, serves as a critical indicator of diabetic nephropathy severity. The excess protein, particularly albumin, leaks into the urine due to glomerular barrier dysfunction and exacerbates tubular damage and fibrosis, further impairing kidney function (13).

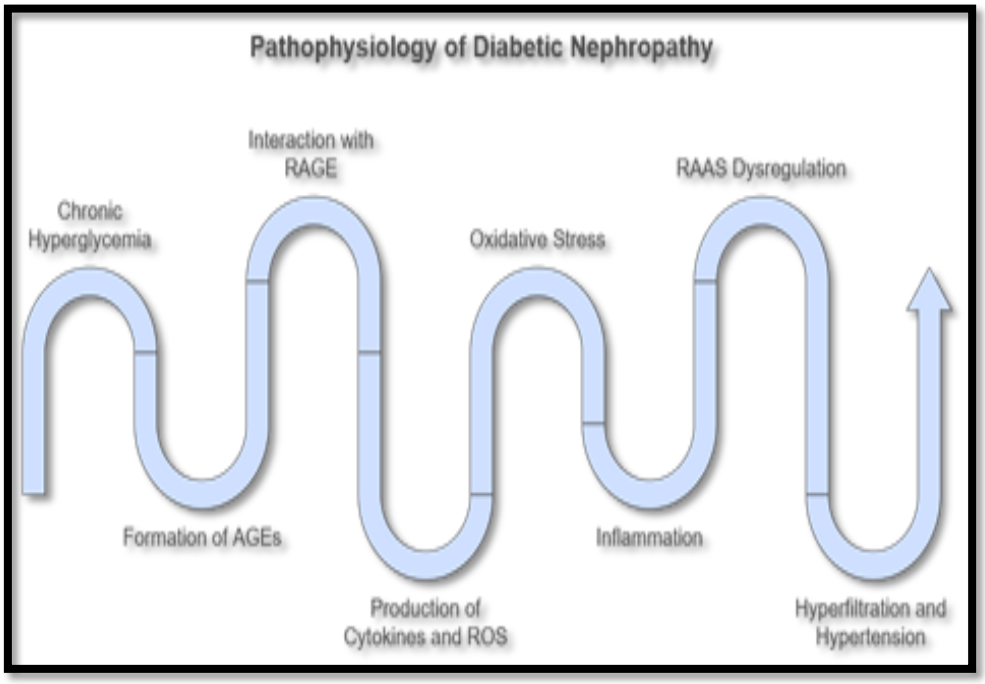


Figure 1: Pathophysiology of Diabetic Nephropathy. (14).

Cytokines

Cytokines are tiny proteins that are released and act as crucial mediators in immunological signalling and regulation. They are responsible for coordinating the complex responses that the body responds to in response to infections, trauma, and inflammation. In addition to being generated by a variety of cells, the majority of which are immune system cells, they play a crucial role in the coordination of immunological and inflammatory responses. They do this by affecting the behaviour of other cells and regulating the connections between them. The creation and release of cytokines are essential components in the regulation of immunity, inflammation, and haematopoiesis, which is the process of blood cell formation. The preservation of physiological homeostasis depends on each of these mechanisms. However, cytokines play a significant part in the emergence of autoimmune disorders, chronic inflammatory diseases, and even cancer when they are not adequately managed,

highlighting the fact that they have a positive and negative impact on both health and disease (15). On the basis of their roles, cytokines may be roughly categorised into a number of different categories. These types include interleukins (ILs), interferons (IFNs), tumour necrosis factors (TNFs), chemokines, and growth factors . There are several levels of complexity added to immune responses as a result of the fact that each category performs a distinct function in immune regulation and inflammation

(16). Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system, leading to cellular damage. In DN, hyperglycemia increases ROS generation through multiple pathways, including mitochondrial dysfunction, activation of NADPH oxidase, and advanced glycation end-product (AGE) formation (17). AGEs are proteins or lipids modified by nonenzymatic glycation, contributing to inflammation, fibrosis, and endothelial dysfunction. Furthermore, oxidative DNA damage, as indicated by elevated levels of 8-hydroxy-2'-deoxyguanosine (8-OHDG), highlights the role of ROS in impairing cellular integrity in DN.Biomarkers such as 8-OHDG, AGEs, and markers of oxidative stress (e.g., malondialdehyde [MDA])(18).These biomarkers not only reflect the underlying oxidative and glycation processes but also correlate with disease severity and progression. Understanding their roles and interrelationships offers valuable insights into the molecular mechanisms of DN and provides opportunities for early diagnosis and targeted therapeutic interventions. This study focuses on evaluating DN severity through the quantification of 8-OHDG, AGEs, and oxidative stress biomarkers, shedding light on their clinical relevance and potential as therapeutic targets.

Materials and Methods:

Patients and data collection

90 diabetic patients, 50 of whom were male and 40 of whom were female, who attended Al-Hussein Teaching Hospital in Nasiriyah between December 2023 and late May 2024 were included in this study. The patients ranged in age from 45 to 82. Five milliliters of fresh venous blood were obtained by puncturing the veins of both patients and healthy volunteers using a disposable medical syringe. After questionnaires were created to correspond with the research samples that were obtained,the samples were gathered.Then the blood was puted in plastic sterile tubes and left at room temperature (20-25)CO to permit it to clot and separate the serum.The samples was placed in a centrifuge to separate the blood and obtain serum,(19). The sophonix device was used, which depends on the principle of its operation on chemiluminescent immunoassay (cLIA) to estimate, MDA (ng/mL) (SunLong Biotech,Germany),AOPP(ng\ml),glucose(mg/dL),HNE(ng\ml), 8-OHdG(pg\ml) and AGEs(ng\ml). These parameters were evaluated according to the ELISA technique

Analysis of quantitative data is frequently done using statistical analysis, which also offers techniques for characterizing data. categorical and continuous data using straightforward reasoning. In order to assess the link between two statistical data sets, the process entails gathering data. Every data point in this study is displayed as a frequency and percentage. Statistical analyses were conducted using SPSS (version 26) and the two-tailed dependent and independent t-tests for normally distributed variables, while the Mann-Whitney *U* and Wilcoxon test and chi-square test were used for non-normally distributed variables. The threshold of 0.05 was deemed statistically significant.
Ethical considerations: The study was approved by the human ethics committee . Everyone who took part in the study was told about it and asked to sign a consent form. The patient was also guaranteed that his information would be kept private.

Results:

The average age of diabetic nephropathy patients was 68.40 ± 9.85 years, while the average age of control participants was 59.48 ± 9.60 years.

Table 1: Comparison between patients and control groups in Age.

Groups	Mean	Std. Deviation	Std. Error of Mean
Patients (No.=90)	68.40	9.85	1.03
Control(No.=45)	59.48	9.60	1.43

Results of oxidative stress biomarker in patients and healthy controls:

Oxidative stress biomarker results in both healthy controls and patients.

Table (1) shows the findings of a comparison of oxidative stress biomarkers (MDA, 8OHDG, AOPP, HNE4, and AGE) between the patient and control groups. Malondialdehyde (MDA) levels in the patient and healthy control groups were 470.26± 47.7 and 275.42± 17.38, respectively; the patient group's mean values were greater than those of the healthy control group, and the difference was significant (P > 0.05). Additionally, the mean levels of 8-hydroxydeoxyguanosine (8-OHDG) were 400.91± 36.11 for the patient group and 150.21± 14.81 for the healthy control group; the difference between the two groups was significant (P > 0.05), with the mean levels of 8-OHDG being higher in the patient group. The current results demonstrate a significant increase in all of these parameters in the patient group when compared to the healthy control group, with a significant difference (P > 0.05) in the mean levels of Advanced Oxidation Protein Products (AOPP), 4-Hydroxynonenal (4-HNE), and Advanced Glycation End Products (AGEs).

Table 2: Comparison between patients and control groups according to some oxidative stress biomarker.

	Groups	MDA	8OHDG	AOPP	4-HNE	AGE
Patients	**Mean**	470.26	400.91	96.67	9.28	470.82
	Std. Deviation	47.7	36.11	12.93	1.10	62.24
	Std. Error of Mean	5.02	5.13	1.99	0.11	7.82
Control	**Mean**	275.42	150.21	49.22	5.27	180.82
	Std. Deviation	17.38	14.81	7.87	0.81	21.67
	Std. Error of Mean	3.06	5.19	1.17	0.11	4.72
	p-value	0.001 † S	0.001 † S	0.001 † S	0.001 † S	0.001 † S

†: Independent T test; **S**: significant at $P < 0.05$

Table 3: Comparison between patient male and patient female according to some oxidative stress biomarker.

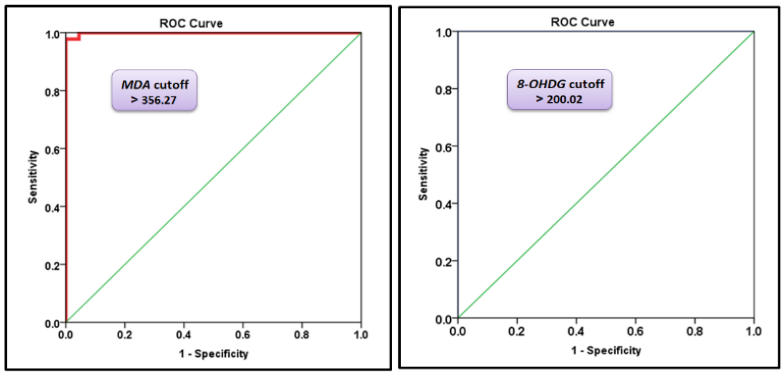
	Groups	MDA	8OHDG	AOPP	4-HNE	AGEs
Male	**Mean**	487.30	403.72	99.56	9.53	518.53
	Std. Deviation	32.96	36.02	13.29	1.21	63.49
	Std. Error of Mean	6.07	7.99	3.29	0.17	15.94
Female	**Mean**	448.96	397.37	93.04	8.97	411.17
	Std. Deviation	25.13	33.27	10.58	0.87	55.64
	Std. Error of Mean	7.13	7.16	1.67	0.13	12.73
	p-value	0.017 † S	0.758 † NS	0.105 † NS	0.076 † NS	0.001 † S

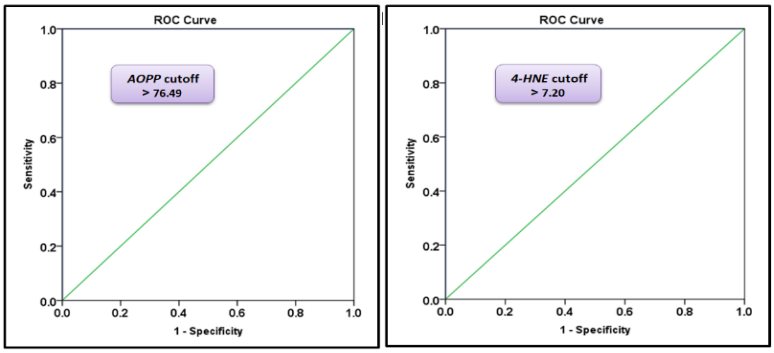
†: Independent T test; S: significant at $P < 0.05$; NS: non-significant at $P > 0.05$

Oxidative stress parameters' receiver operator characteristic (ROC) outcome. Receiver operator characteristic (ROC) curve analysis was used to assess the cutoff value of oxidative stress parameters and predict diabetic nephropathy disease as diagnostic or adjuvant diagnostic tests. The findings are displayed in table (4) and figure (2).

Table 4: ROC and AUC analysis of the measured parameters for diagnosis

Parameters	Cut-off	Sensitivity %	Specificity %	AUC (95% CI)	P value
MDA	> 356.27	98.9 %	97.8 %	0.999 (0.997-1.000)	< 0.001
8-OHDG	> 200.02	100.0%	100.0%	1.000 (1.000-1.000)	< 0.001
AOPP	> 76.49	100.0 %	100.0 %	1.000 (1.000-1.000)	< 0.001
4-HNE	> 7.20	100.0%	100.0%	1.000 (1.000-1.000)	< 0.001
AGEs	> 225.28	97.8%	97.8%	0.996 (0.989-1.000)	< 0.001





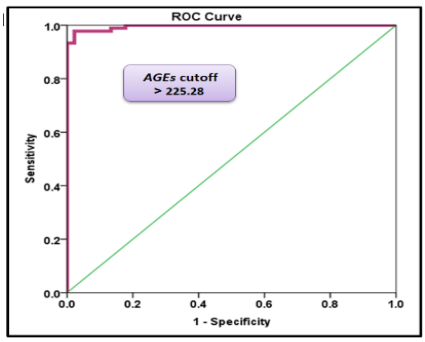


Figure 2: (A) Receiver operating characteristic curve for MDA levels to distinguish patients with diabetic nephropathy from healthy control subjects. (B) Receiver operating characteristic curve for 8-OHDG levels to distinguish patients with diabetic nephropathy from healthy control subjects. (C) Receiver operating characteristic curve for AOPP levels to distinguish patients with diabetic nephropathy from healthy control subjects. (D) Receiver operating characteristic curve for 4-HNE levels to distinguish patients with diabetic nephropathy from healthy control subjects. (E) Receiver operating characteristic curve for AGEs levels to distinguish patients with diabetic nephropathy from healthy control subjects.

correlation between diabetic nephropathy patients' oxidative stress metrics:

Tables (5) displayed the relationships between oxidative stress indicators in diabetic nephropathy patients. In individuals with diabetic nephropathy, MDA levels and 4-HNE levels (r=0.293 and p=0.005), AGE levels and 4-HNE (r=0.209 and p=0.048), and AOPP levels and

4-HNE levels (r=0.351 and p=0.001) are all positively correlated. However, the current findings indicate that there is no significant association between any of the other factors.

Biomarker	oxidative stress biomarker									
	MDA		8-OHDG		AOPP		4-HNE		AGEs	
	R	*P*	*R*	*P*	*r*	*P*	*R*	*P*	*r*	*p*
MDA	1									
8-OHDG	0.061	0.4568	1							
AOPP	0.129	0.225	0.121	0.256	1					
4-HNE	0.293	0.005*	0.005	0.966	0.351	0.001*	1			
AGEs	0.042	0.695	0.135	0.205	0.076	0.475	0.209	0.048*	1	

Table 5: Correlation between oxidative stress biomarker in patients with diabetic nephropathy

r: correlation coefficient.

Discussion:

This study demonstrated a substantial rise in biomarker levels (MDA, 8OHDG, AOPP, HNE4, and AGE) by gathering and comparing measurements for individuals with diabetic kidney disease. Diabetic nephropathy, also referred to as diabetic kidney disease, is the primary cause of end-stage renal disease (ESRD) worldwide and a serious microvascular consequence of diabetes.Its pathophysiology is complex and involves multiple intertwined mechanisms, including hyperglycemia, oxidative stress, inflammation, hemodynamic abnormalities, and genetic factors (20). Chronic hyperglycemia is a key driver in the pathogenesis of diabetic nephropathy, leading to the accumulation of advanced glycation end products (AGEs). AGEs form through non-enzymatic reactions between glucose and proteins, lipids, or nucleic acids, which cause structural and functional changes in these molecules. The buildup of AGEs in renal tissues, particularly in glomerular and tubular cells, triggers cellular dysfunction, abnormal tissue remodeling, and heightened inflammatory responses. The interaction of AGEs with their receptor, known as RAGE, on renal cells stimulates the production of pro-inflammatory cytokines and reactive oxygen species (ROS), further contributing to kidney damage (9). Oxidative stress plays a central role in diabetic nephropathy and results from an imbalance between ROS production and the body's antioxidant defenses. This imbalance leads to cellular injury, inflammation, and fibrosis within kidney tissue. Oxidative stress disrupts normal cellular functions and accelerates fibrosis by increasing the synthesis of extracellular matrix proteins, which accumulate in glomerular and tubulointerstitial compartments, resulting in tissue remodeling and loss of renal function (10).

Conclusion:

The findings of this study underscore the importance of 8-OHDG, AGEs, and oxidative stress biomarkers in evaluating diabetic nephropathy (DN) severity. Elevated 8-OHDG levels reflect oxidative DNA damage, a hallmark of cellular injury caused by hyperglycemia-induced ROS. Similarly, increased AGEs concentrations are indicative of prolonged glycation and oxidative stress, which exacerbate kidney damage through inflammation and fibrosis. Markers of oxidative stress, including MDA, SOD, and TAC. further clarify how the pro-oxidant and antioxidant systems are out of balance in the pathophysiology of DN.

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