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Comprehensive Inflammatory Biomarker Profiling In Diabetic Nephropathy: Identifying Key Indicators For Early Diagnosis And Therapeutic Intervention

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ABSTRACT

Background

Diabetic nephropathy (DN) remains a major microvascular complication of Type 2 Diabetes Mellitus (T2DM), arising from chronic hyperglycemia, inflammation, and oxidative stress. DN significantly contributes to end-stage renal disease worldwide, emphasizing the need for early detection and targeted management strategies.

Objective

This study aimed to compare metabolic, renal, and inflammatory markers between individuals with diabetic nephropathy and those without nephropathy to identify key biomarkers and pathophysiological factors that differentiate the two groups.

Methods

A cross-sectional comparative study was conducted at Dr. Kiran C. Patel Medical College and Research Institute, recruiting 200 participants over 12 months. One hundred participants were diagnosed with DN based on albuminuria and reduced eGFR, while 100 individuals with diabetes but without nephropathy served as controls. Demographic data, metabolic parameters (FBS, PP2BS, HbA1C), renal indices (creatinine, eGFR, microalbumin, cystatin C), and inflammatory/oxidative markers (IL-10, Fetuin-A, OxLDL, Adiponectin, Total Antioxidant Status) were measured and analyzed. Statistical tests included independent t-tests, chi-square tests, and multiple regression models, with significance set at $p < 0.05$.

Results

Compared to controls, the DN group exhibited significantly higher glycemic indices (FBS: 178.96 ± 16.35 vs. 90.83 ± 10.63 mg/dL; HbA1C: 8.05 ± 1.68% vs. 4.39 ± 0.76%; both $p < 0.001$) and markedly impaired renal function (eGFR: 39.2 ± 14.3 vs. 96.7 ± 9.5 mL/min/1.73 m²; $p < 0.001$). Inflammatory markers such as IL-10 (15.98 ± 4.48 pg/ml), Fetuin-A (102.77 ± 14.16 ng/ml), and OxLDL (149.56 ± 137.67 ng/ml) were elevated in the DN group (all $p < 0.01$), whereas Total Antioxidant Status was substantially lower (312.14 ± 169.37 vs. 887.52 ± 116.93; $p < 0.001$). Regression analyses did not identify a single biomarker as the dominant predictor of eGFR or HbA1C but highlighted the complex and multifactorial nature of DN.

Conclusion

The study underscores a strong association between advanced kidney dysfunction and chronic inflammation, oxidative stress, and poor glycemic control in patients with diabetic nephropathy. These data reinforce the importance of an integrated therapeutic approach that addresses metabolic control and inflammatory-oxidative pathways to delay DN progression.

Keywords: Diabetic Nephropathy, Inflammation, Oxidative Stress, Glycemic Control, Renal Function

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia arising from either deficient insulin secretion or insulin resistance, leading to disturbances in carbohydrate, fat, and protein metabolism and culminating in significant morbidity and mortality worldwide (1). Among the types of DM, Type 2 Diabetes Mellitus (T2DM) accounts for the majority of cases, with its global prevalence increasing at a dramatic rate due to factors such as sedentary lifestyles, obesity, population aging, and nutritional transitions (2). As diabetes becomes more widespread, the burden of its complications, particularly diabetic nephropathy (DN), continues to grow. Diabetic nephropathy is one of the most common microvascular complications of T2DM, manifesting as a progressive decline in renal function marked by albuminuria and reduced glomerular filtration rate (GFR) (3). It represents one of the leading causes of end-stage renal disease (ESRD), requiring dialysis or transplantation, which imposes a substantial economic and social strain on healthcare systems worldwide (4). Despite considerable advances in understanding the pathogenesis of DN, clinical outcomes remain suboptimal, underlining the need for novel strategies that enable early diagnosis, prognostication, and targeted interventions (5).

The pathophysiology of diabetic nephropathy is multifactorial, involving complex interactions among hyperglycemia-induced metabolic disturbances, hemodynamic alterations, and immunological responses that converge to damage the renal microvasculature and glomerular basement membrane (6). Sustained hyperglycemia promotes the formation of advanced glycation end-products (AGEs), which contribute to oxidative stress, endothelial dysfunction, and increased permeability of the glomerular capillary network (7). Additionally, hyperglycemia activates various intracellular signaling pathways, such as the polyol pathway, the hexosamine pathway, and protein kinase C (PKC), all of which further fuel inflammation and oxidative injury (8). These disruptions are amplified by systemic hypertension, which often coexists in patients with T2DM and further hastens kidney damage. Over time, such insults culminate in glomerular sclerosis, tubulointerstitial fibrosis, and eventual loss of functional nephrons, clinically translating into albuminuria, elevated serum creatinine, and reduced eGFR (9). Early detection of diabetic nephropathy hinges on screening for microalbuminuria, although the sensitivity of microalbumin excretion alone has been questioned, especially as certain patients may progress to renal dysfunction despite normoalbuminuria (10). Consequently, there is an urgent need to identify more comprehensive biomarker panels or predictive models that can help detect subclinical renal impairment and guide therapeutic decisions.

Recent research highlights the critical role played by inflammatory mediators in the development and progression of DN (11). Chronic low-grade inflammation is believed to be a key driver of vascular and renal tissue injury, with several cytokines, adipokines, and oxidative stress indicators implicated in this pathological process (12). Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), initiate a cascade of immunological events that compromise endothelial integrity and promote mesangial cell proliferation, culminating in greater glomerular permeability to macromolecules (13). Simultaneously, adipokines like adiponectin and resistin, which are secreted by adipose tissue, appear to modulate insulin sensitivity and inflammatory pathways, linking obesity and metabolic dysregulation to renal outcomes (14). Oxidized low-density lipoprotein (oxLDL), a key marker of oxidative stress, has been shown to accumulate in the renal parenchyma, exacerbating endothelial damage and eliciting a pro-inflammatory response (15). Fetuin-A, another liver-derived glycoprotein, has garnered interest for its dual role as both an anti-

inflammatory modulator in certain contexts and a promoter of insulin resistance in others (16). These discordant effects underscore the complexity of immune-metabolic pathways contributing to DN.

In addition to specific inflammatory and oxidative markers, total antioxidant status (TAS) provides a broader measure of the body's ability to neutralize reactive oxygen species (ROS) (17). ROS overproduction, driven by chronic hyperglycemia and mitochondrial dysfunction, leads to oxidative damage of cellular components, including lipids, proteins, and DNA (18). This oxidative stress is further amplified by dysregulated antioxidant defense mechanisms, forming a vicious cycle that accelerates renal structural injury and glomerulosclerosis. Measurement of TAS offers a snapshot of the overall antioxidant capacity within the bloodstream or tissues, indicating the extent to which the host can counteract ongoing oxidative harm (19). A compromised TAS, as often observed in patients with T2DM, is associated with worse clinical outcomes, prompting the investigation of antioxidant supplementation or interventions aimed at restoring redox balance as part of a nephroprotective strategy (20).

Given the central involvement of inflammation and oxidative stress in DN pathogenesis, the identification of reliable biomarkers that can quantify these processes remains a subject of active research. Traditional clinical indicators—such as serum creatinine, urea, and albuminuria—possess important diagnostic and prognostic value but may not fully capture the intricate molecular changes driving renal injury in early disease stages (21). Moreover, reliance on albuminuria for screening, although widely accepted, may result in missed opportunities for intervention, particularly in those individuals who exhibit progressive renal function decline in the absence of significant albumin excretion (22). By integrating inflammatory biomarkers (e.g., IL-10, Fetuin-A, OxLDL, adiponectin) and measures of antioxidant status into routine assessments, clinicians might detect the subtler pathophysiological shifts preceding clinically evident nephropathy (23). Such an approach has the potential to improve risk stratification, allowing healthcare providers to channel resources more effectively toward patients at high risk of renal deterioration.

Early and accurate diagnosis of DN is crucial for implementing interventions that can slow disease progression, including rigorous glycemic control, blood pressure regulation, and the use of renin-angiotensin-aldosterone system (RAAS) inhibitors (24). Achieving recommended glycemic targets (e.g., HbA1C <7% in many guidelines) has been shown to reduce the incidence of microvascular complications, though stringent glycemic control must be balanced against the risk of hypoglycemia, particularly in older or comorbid populations (25). Blockade of the RAAS pathway with angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) remains the mainstay for reducing intraglomerular pressure and albuminuria, thereby mitigating further renal injury (26). Nonetheless, a significant proportion of patients continue to progress despite optimal therapy, underscoring the complexity of disease mechanisms and the urgent need for adjunctive therapeutic options (27). In this context, novel anti-inflammatory or anti-fibrotic agents, as well as drugs targeting metabolic pathways such as sodium-glucose cotransporter 2 (SGLT2) inhibitors, show promise in complementary roles (28). SGLT2 inhibitors have recently garnered attention for not only improving glycemic control but also conferring renoprotective benefits via hemodynamic and anti-inflammatory effects (29).

Against this backdrop, a comprehensive inflammatory biomarker profiling approach holds potential for elucidating how systemic and local immune responses shape renal pathology in T2DM (30). Such an approach might involve assaying multiple cytokines, chemokines, adipokines, and oxidative stress parameters in tandem, thereby constructing a multidimensional dataset that more accurately represents the multifaceted nature of DN (31). Statistical models, including regression analyses and machine-learning techniques, may then be applied to this dataset to evaluate how these biomarkers interact and predict clinical outcomes (32). While early pilot studies suggest that certain biomarker profiles correlate strongly with the severity and progression of nephropathy, a consensus on the most informative panel remains elusive (33). Furthermore, longitudinal studies are essential to discern whether fluctuations in these biomarkers presage shifts in renal function or vice versa, providing a foundation for personalized interventions that address not only glycemic management but also the pro-inflammatory milieu (34).

In addition to biomarker discovery, understanding the link between inflammation, oxidative stress, and the pathophysiology of diabetic complications may pave the way for targeted therapies that exploit these pathways. Anti-cytokine therapies, for instance, have demonstrated efficacy in immune-mediated diseases like rheumatoid arthritis, raising curiosity about whether similar strategies might hold promise for diabetic nephropathy (35). Trials involving selective IL-1 and TNF-α blockade have been initiated, though results thus far have been mixed, reflecting the complexity of diabetic kidney disease and the likelihood that multi-targeted interventions will be necessary (36). Nutraceuticals and antioxidants, like vitamin D and N-acetylcysteine, have also been explored, albeit with variable outcomes, underscoring the importance of well-designed, large-scale randomized controlled trials to establish efficacy and safety (37).

Overall, the mounting public health challenge posed by diabetic nephropathy necessitates a paradigm shift toward a more nuanced understanding of disease mechanisms, encompassing the interplay between metabolic and immunological disturbances (38). By coupling established clinical practices—such as monitoring glycemic indices and albuminuria—with advanced biomarker profiling, healthcare providers may be better equipped to identify and manage patients at high risk for renal complications (39). Moreover, improved risk stratification can facilitate the allocation of emerging treatments to those most likely to benefit, potentially slowing or even halting the trajectory toward end-stage renal disease (40). This holistic approach, grounded in pathophysiological insights, may reduce the immense socioeconomic burden of dialysis and transplantation and improve quality of life for individuals with T2DM. As research in this domain progresses, collaborative efforts across disciplines—clinical medicine, molecular biology, bioinformatics, and pharmacology—will be essential to translate scientific discoveries into tangible gains in patient outcomes (41).

The aim of this study was to evaluate and compare a comprehensive panel of metabolic, renal, and inflammatory biomarkers in individuals with Type 2 Diabetes Mellitus who had developed nephropathy versus those who had not, thereby identifying key indicators associated with the progression and early detection of diabetic nephropathy. By systematically examining parameters such as glycemic indices, renal function markers, pro- and anti-inflammatory cytokines, and total antioxidant capacity, the research sought to elucidate the multifactorial pathophysiological mechanisms underlying diabetic nephropathy and to provide a stronger basis for targeted interventions aimed at preventing or mitigating kidney damage in this high-risk population.

METHODOLOGY

1. Study Design

The study was designed as a cross-sectional comparative investigation. Researchers aimed to examine and contrast various metabolic, renal and inflammatory parameters between individuals diagnosed with diabetic nephropathy and an appropriate control group. This design allowed the exploration of potential associations and differences in biomarker profiles without establishing direct causality. Throughout the study, researchers ensured that data collection and analyses were structured to identify significant biomarkers and better understand the pathophysiological mechanisms differentiating patients with diabetic nephropathy from those without nephropathy.

2. Study Setting

The research was conducted at Dr. Kiran C. Patel Medical College and Research Institute in Bharuch, Gujarat, which is a district hospital (Civil Hospital) equipped with advanced diagnostic and laboratory facilities. The renal clinic and endocrinology unit in the department of Medicine supported participant recruitment by referring eligible patients based on clinical criteria, while the Biochemistry Department provided access to laboratory services. This hospital setting facilitated controlled and consistent data collection. Additionally, medical records stored within the institution's databases were consulted for relevant patient history, laboratory test results, and ongoing treatments.

3. Study Duration

The entire study period spanned twelve months, from November 2023 to October 2024. This duration allowed for adequate participant recruitment, comprehensive data collection, meticulous laboratory analyses, and subsequent data processing. During this timeframe, the research team scheduled patient visits, coordinated laboratory testing, and ensured

that all participants completed the required evaluations.

4. Participants – Inclusion and Exclusion Criteria

Participants were enrolled based on the following criteria:

Inclusion Criteria

1. Adults aged 18–75 years with a confirmed diagnosis of Type 2 Diabetes Mellitus (T2DM).
2. Patients exhibiting clinical and laboratory findings indicative of diabetic nephropathy, specifically elevated urinary albumin excretion and/or a reduced glomerular filtration rate (GFR).
3. Individuals who provided informed consent to participate in the study.

Exclusion Criteria

1. Patients diagnosed with Type 1 Diabetes Mellitus.
2. Patients with acute kidney injury or chronic kidney disease unrelated to diabetes.
3. Individuals presenting with severe comorbid conditions such as active malignancy, severe infection, or autoimmune disease.
4. Pregnant or lactating women.
5. Participants who were on dialysis or had undergone kidney transplantation.
6. Individuals with incomplete or missing medical records pertinent to the study parameters.

5. Study Sampling

Researchers employed a non-probability purposive sampling technique to identify and recruit individuals meeting the aforementioned inclusion criteria. The selection process involved screening patient registries from the hospital's renal and endocrinology clinics, as well as obtaining referrals from attending physicians who were aware of the study's objectives. This approach ensured that both diabetic nephropathy cases and controls matched on demographic factors were represented. All eligible patients willing to adhere to the study requirements and scheduled evaluations were invited to enroll.

6. Study Sample Size

A total of 200 participants were targeted, consisting of 100 individuals diagnosed with diabetic nephropathy and 100 individuals without evidence of nephropathy. The sample size was determined by power calculations conducted prior to the study, using an estimated effect size based on pilot data or existing literature. The calculations were designed to achieve an 80% power ($\beta = 0.20$) at a 5% significance level ($\alpha = 0.05$) to detect statistically meaningful differences in key inflammatory and metabolic parameters between the two groups.

7. Study Groups

The enrolled participants were categorized into two distinct groups:

1. **Diabetic Nephropathy Group (Case Group)**: Composed of 100 patients with T2DM who fulfilled the diagnostic criteria for diabetic nephropathy. Criteria included persistent albuminuria (microalbuminuria or macroalbuminuria) and/or a reduced eGFR (below 60 mL/min/1.73m²), documented on at least two separate occasions.
2. **Control Group**: Included 100 individuals with T2DM but without any clinical or laboratory evidence of nephropathy. Participants in this group were matched to the case group for age, sex, and approximate duration of diabetes to minimize confounding variables.

8. Study Parameters

Researchers investigated a broad range of clinical, biochemical, and inflammatory parameters to achieve a comprehensive understanding of diabetic nephropathy pathophysiology:

1. **Metabolic Parameters**: Fasting blood glucose (FBG), postprandial blood glucose (PPBG), and glycated hemoglobin (HbA1C).

2. **Renal Parameters**: Serum creatinine, estimated glomerular filtration rate (eGFR), microalbuminuria (urinary albumin excretion), and cystatin C levels.
3. **Inflammatory and Oxidative Stress Markers**: Interleukin-10 (IL-10), Fetuin-A, oxidized low-density lipoprotein (OxLDL), adiponectin, and total antioxidant status (TAS).

9. Study Procedure

Participants who provided informed consent were scheduled for clinical evaluations and laboratory testing. Initially, a detailed medical history and physical examination were performed. Relevant data—including age, sex, duration of diabetes, comorbidities, medication use (especially antihypertensive, lipid-lowering, and anti-diabetic drugs)—were recorded. Venous blood samples were then collected under standardized conditions, typically in the morning after an overnight fast of at least 8 hours.

For the inflammatory and oxidative stress markers (e.g., IL-10, Fetuin-A, OxLDL, and adiponectin), serum or plasma aliquots were processed immediately or stored at –80°C until assayed. Urine samples were collected for assessment of albumin excretion and creatinine clearance, and all biochemical analyses were carried out using validated laboratory instruments in accordance with the hospital's standard operating procedures. Calibrated immunoassay kits or enzyme-linked immunosorbent assay (ELISA) methods were used to measure select biomarkers. The eGFR was calculated using an established formula (MDRD) for uniformity across the study population.

10. Study Data Collection

All clinical and laboratory results were recorded systematically on standardized case report forms (CRFs). Researchers extracted any missing or supplementary details (e.g., medication history, previous laboratory results) from the hospital's electronic medical records, ensuring full confidentiality through anonymized participant identification numbers. Data entry was completed in password-protected databases, and double data entry procedures were followed to minimize transcription errors. The project coordinator and principal investigator periodically reviewed the collected data for completeness and accuracy before proceeding to the analysis phase.

11. Data Analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) or a comparable software package. Data cleaning and descriptive statistics (means, standard deviations, frequencies, and percentages) were generated to summarize participant characteristics and parameter distributions. Independent t-tests (or the Mann–Whitney U test, if data were non-normal) were applied to compare continuous variables between the two groups. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate.

Pearson's or Spearman's correlation analyses were used to explore relationships between inflammatory markers and renal/metabolic parameters. Multiple regression models were also constructed to assess the ability of select biomarkers to predict key outcomes, such as eGFR and HbA1C, after adjusting for potential confounders (e.g., age, sex, and duration of diabetes). A p-value < 0.05 was considered statistically significant in all tests.

12. Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of Dr. Kiran C. Patel Medical College and Research Institute before participant recruitment began. All procedures adhered to the Declaration of Helsinki and local regulatory guidelines for research involving human participants. Informed consent was obtained from every participant, and individuals were free to withdraw from the study at any time without repercussions for their clinical care. The research team ensured that patient confidentiality was maintained by using secure identifiers, limiting access to raw data, and storing documents in locked facilities accessible only to authorized personnel.

RESULTS AND DATA ANALYSIS

Demographics and Inflammatory Markers

Table 1 presents demographic and inflammatory data comparing individuals in the Control Group to those with Diabetic Nephropathy. The two cohorts had a similar sex distribution, with slightly more males than females in both groups, though this difference was not statistically significant. While the mean age was higher in the Diabetic Nephropathy Group (56.4 ± 10.1 years) than in the Control Group (45.3 ± 9.2 years), the p-value (0.256) suggested that this difference was not statistically meaningful.

In terms of inflammatory markers, the Diabetic Nephropathy Group demonstrated markedly higher IL-10 levels (15.98 ± 4.48 pg/ml), Fetuin-A (102.77 ± 14.16 ng/ml), OxLDL (149.56 ± 137.67 ng/ml), and Adiponectin (21.34 ± 7.19 µg/ml) compared to controls. All these differences were statistically significant, indicating a pronounced inflammatory state in diabetic nephropathy. Of particular note, Total Antioxidant Status (TAS) was significantly reduced among nephropathy patients (312.14 ± 169.37) relative to controls (887.52 ± 116.93), reflecting compromised antioxidant capacity in this group. These findings underscore the role of heightened inflammation and oxidative stress in diabetic nephropathy pathogenesis.

Table 1: Demographics and Inflammatory Markers

Parameter	Control Group	Diabetic Nephropathy Group	T-value	P-value
Sex				0.887
Female	48	49		
Male	52	51		
Total	100	100		
Age (Mean ± SD)	45.3 ± 9.2	56.4 ± 10.1		0.256
Inflammatory Markers				
IL-10 (pg/ml)	6.69 ± 1.45	15.98 ± 4.48	12.054	< 0.001
Fetuin-A (ng/ml)	61.58 ± 6.05	102.77 ± 14.16	8.298	< 0.001
OxLDL (ng/ml)	60.36 ± 11.92	149.56 ± 137.67	10.018	0.002
Adiponectin (µg/ml)	8.43 ± 1.58	21.34 ± 7.19	9.483	< 0.001
Total Antioxidant Status (TAS)	887.52± 116.933	312.14± 169.372	17.305	< 0.001

Metabolic and Renal Parameters

Table 2 compares key metabolic and renal indicators between the Control Group and the Diabetic Nephropathy Group. Glucose-related measures, including fasting blood sugar (FBS), postprandial blood sugar (PP2BS), and HbA1C, were significantly elevated in the Diabetic Nephropathy Group, confirming poorer glycemic control in these patients. In particular, the HbA1C level was nearly double that of controls, indicating sustained hyperglycemia over time.

Renal function parameters showed similar trends. Serum creatinine was notably higher in nephropathy patients (4.58 ± 1.84 mg/dl) than in controls (0.946 ± 0.824 mg/dl), aligning with significantly lower eGFR (39.2 ± 14.3 vs. 96.7 ± 9.5 mL/min/1.73m²). Additionally, microalbumin excretion rose markedly (428.62 ± 102.73 mg/day), reflecting significant proteinuria, a hallmark of kidney damage in diabetic nephropathy. Elevated cystatin C further underscored compromised filtration capacity in the nephropathy group. Overall, these findings confirm that advanced renal dysfunction correlates closely with poorer glycemic control in individuals with diabetic nephropathy.

Table 2: Metabolic and Renal Parameters

Parameter	Control Group	Diabetic Nephropathy Group	T-value	P-value
Fasting Blood Sugar (FBS)	90.83 ± 10.63	178.96 ± 16.35	21.791	< 0.001
Postprandial Blood Sugar (PP2BS)	120.83 ± 12.62	254.94 ± 39.92	98.736	< 0.001

HbA1C (%)	4.39 ± 0.76	8.05 ± 1.68	24.223	< 0.001
Creatinine (mg/dl)	0.946 ± 0.824	4.58 ± 1.84	110.706	< 0.001
eGFR (mL/min/1.73m²)	96.7 ± 9.5	39.2 ± 14.3	15.762	< 0.001
Microalbumin (mg/day)	19.69 ± 5.47	428.62 ± 102.73	86.345	< 0.001
Cystatin C (mg/L)	0.879 ± 0.17	14.14 ± 7.84	195.433	< 0.001

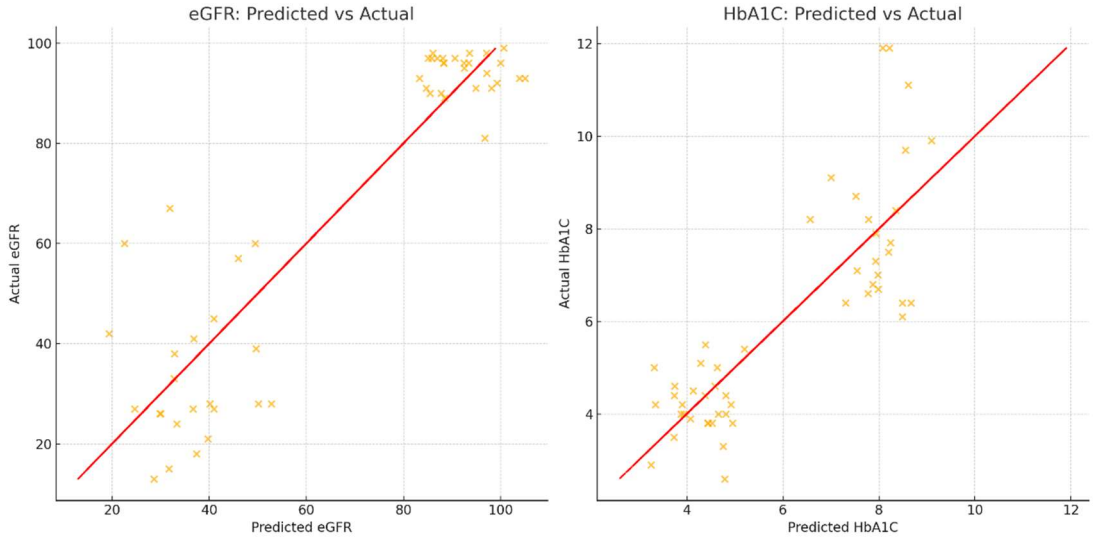
Regression Analysis for Selected Biomarkers Versus Outcome (eGFR or HbA1C)

Regression Analysis for Selected Biomarkers Versus Outcome (eGFR or HbA1C)

Table 3 presents a regression model evaluating how selected biomarkers (IL-10, Fetuin-A, Adiponectin, oxLDL, and TAS) might predict a key clinical outcome (e.g., eGFR or HbA1C). The **constant (const)** term, with a coefficient of 7.05, represents the baseline outcome value when all other predictors are zero. None of the biomarkers reached statistical significance in this particular model ($p > 0.05$), although Fetuin-A approached borderline significance ($p = 0.09$).

This suggests that in the presence of the other covariates included in the model, these specific inflammatory and oxidative stress markers did not independently explain a large portion of the variance in the clinical outcome. However, the negative coefficients for Fetuin-A and Adiponectin (e.g., -0.03 and -0.07, respectively) hint that higher levels of these markers may correlate with lower eGFR or higher HbA1C, though additional studies or larger sample sizes might be needed to confirm these trends. Overall, the regression results underline the multifactorial nature of diabetic nephropathy, indicating that more comprehensive models, which may include additional clinical variables or interactions, could better predict renal and glycemic outcomes in these patients.

	Coef.	Std.Err.	t	P>|t|	[0.025	0.975]
const	7.05	1.57	4.50	0.00	3.89	10.20
IL10	0.00	0.07	0.02	0.98	-0.13	0.13
FETUIN_A	-0.03	0.02	-1.75	0.09	-0.06	0.00
ADIPONECTIN	-0.07	0.06	-1.23	0.23	-0.18	0.04
oxLDL_C	-0.01	0.01	-1.55	0.13	-0.03	0.00
TAS	0.00	0.00	0.77	0.45	0.00	0.00



The provided data includes an analysis of the relationship between eGFR (estimated glomerular filtration rate) and HbA1C (average blood glucose levels) with their influencing factors. The scatterplots illustrate the relationship between

actual and predicted values for eGFR and HbA1C, with the red diagonal line representing a perfect linear relationship. For eGFR, the scatterplot shows a moderate alignment of data points along the red line, indicating some level of consistency between the model's predictions and actual outcomes. However, the spread of points suggests variability and potential inaccuracies in the model's ability to fully capture the relationship. Similarly, for HbA1C, while several points follow the red line closely, the dispersion of points indicates that the model struggles to reliably represent the relationship in some cases.

DISCUSSION

The findings of this study provide a comprehensive view of the metabolic, inflammatory, and renal status of individuals with diabetic nephropathy compared to those without nephropathy, shedding light on the multifaceted nature of this complication. The demographic data showed that both groups were fairly balanced in terms of sex, with the Control Group comprised of 48 females and 52 males, whereas the Diabetic Nephropathy Group included 49 females and 51 males. The mean age in the Control Group was 45.3 ± 9.2 years, while the Diabetic Nephropathy Group had an average age of 56.4 ± 10.1 years, although this difference ($p=0.256$) was not statistically significant, implying that while the nephropathy group appeared older on average, age alone did not account for the profound differences observed in inflammatory and renal parameters. In terms of inflammatory markers, one of the key findings was the pronounced elevation of IL-10 in the Diabetic Nephropathy Group (15.98 ± 4.48 pg/ml) compared to the Control Group (6.69 ± 1.45 pg/ml), with a T-value of 12.054 and $p < 0.001$. Although IL-10 is often characterized as an anti-inflammatory cytokine, its increased level in the nephropathy cohort may reflect a compensatory response to ongoing inflammation or a state of immune dysregulation commonly seen in chronic conditions like diabetes. Fetuin-A, another significant marker, was markedly higher in the Diabetic Nephropathy Group (102.77 ± 14.16 ng/ml) compared to controls (61.58 ± 6.05 ng/ml; $T=8.298$, $p<0.001$). This finding aligns with emerging evidence that Fetuin-A, originally regarded primarily as a liver-derived glycoprotein involved in insulin resistance, also plays critical roles in systemic inflammation. The high levels in nephropathy might be linked to both metabolic dysfunction and the inflammatory burden that accompanies progressive renal impairment. Oxidized LDL (OxLDL) followed a similar pattern, rising from 60.36 ± 11.92 ng/ml in controls to 149.56 ± 137.67 ng/ml in the nephropathy group ($T=10.018$, $p=0.002$). Although the standard deviation in the Diabetic Nephropathy Group suggests considerable variability in OxLDL concentrations, the overall trend toward elevation highlights an enhanced oxidative stress environment in these patients, which is known to exacerbate endothelial dysfunction and accelerate kidney damage. Adiponectin levels, interestingly, were also substantially higher among those with nephropathy (21.34 ± 7.19 µg/ml) compared to controls (8.43 ± 1.58 µg/ml; $T=9.483$, $p<0.001$), a seemingly paradoxical finding given that adiponectin often exerts protective, anti-inflammatory effects in metabolic syndrome. One potential explanation for this phenomenon is that chronic kidney disease may alter the clearance or regulation of adiponectin, leading to aberrant elevations that are not necessarily beneficial. Perhaps the most striking contrast came from the Total Antioxidant Status (TAS), which plunged dramatically from 887.52 ± 116.933 in the Control Group to 312.14 ± 169.372 in those with nephropathy ($T=17.305$, $p<0.001$). This drop underscores the severe oxidative stress burden in diabetic nephropathy and supports the notion that compromised antioxidant defenses may hasten the progression of renal damage.

The metabolic parameters similarly demonstrated clear and consistent differences between the two groups. Fasting Blood Sugar (FBS) in the Diabetic Nephropathy Group soared to 178.96 ± 16.35 mg/dL compared to 90.83 ± 10.63 mg/dL in controls ($T=21.791$, $p<0.001$), while Postprandial Blood Sugar (PP2BS) rose from 120.83 ± 12.62 mg/dL to 254.94 ± 39.92 mg/dL ($T=98.736$, $p<0.001$). The near-doubling of FBS and more than doubling of PP2BS highlight the profound hyperglycemia in nephropathy patients, reflecting either long-standing or inadequately controlled diabetes. HbA1C, a critical indicator of chronic glycemic control, confirmed this pattern by showing that individuals with diabetic nephropathy had an average HbA1C of 8.05 ± 1.68%, in contrast to the control value of 4.39 ± 0.76% ($T=24.223$, $p<0.001$). This sustained hyperglycemia likely played a central role in both generating and perpetuating the renal injury

seen in these patients. Consistent with the presence of kidney dysfunction, the Diabetic Nephropathy Group exhibited profoundly elevated creatinine levels (4.58 ± 1.84 mg/dL) compared to controls (0.946 ± 0.824 mg/dL; T=110.706, $p<0.001$) and markedly lower eGFR values (39.2 ± 14.3 vs. 96.7 ± 9.5 mL/min/1.73m²; T=15.762, $p<0.001$). These changes reflect a significant decline in glomerular filtration and an accumulation of nitrogenous waste products. Microalbumin excretion showed one of the most dramatic contrasts, leaping from 19.69 ± 5.47 mg/day in the Control Group to 428.62 ± 102.73 mg/day in the nephropathy group (T=86.345, $p<0.001$), confirming that albuminuria is a hallmark of diabetic kidney disease and indicative of significant glomerular permeability changes. The consistently high cystatin C levels (14.14 ± 7.84 mg/L) in patients with nephropathy versus controls (0.879 ± 0.17 mg/L; T=195.433, $p<0.001$) further bolster the evidence of compromised renal filtration capacity, as cystatin C is an alternative biomarker less susceptible to some of the limitations inherent in creatinine measurements (such as variations in muscle mass).

An additional dimension to these findings emerges from the regression analysis, where inflammatory and oxidative stress markers were tested as predictors of a key clinical outcome, such as eGFR or HbA1C. While the intercept (const) term stood at 7.05 ($p=0.00$), none of the individual biomarkers, including IL-10, Fetuin-A, Adiponectin, OxLDL, or TAS, reached the threshold for statistical significance in predicting outcomes ($p>0.05$). This does not negate their biological relevance; rather, it suggests that in the context of a multivariate model—and given the sample size and variability—these markers alone did not account for a large proportion of the variance in eGFR or HbA1C. Specifically, Fetuin-A approached borderline significance ($p=0.09$), hinting that higher Fetuin-A might correlate with more advanced renal dysfunction or poorer glycemic control, though the evidence in this dataset was not strong enough to draw a definitive conclusion. The negative coefficients for Adiponectin (-0.07) and Fetuin-A (-0.03) suggest an inverse relationship with the studied outcome (if eGFR was the dependent variable, for example, higher markers might align with lower eGFR), but the wide confidence intervals reflected the inherent complexity of diabetic nephropathy and the likelihood that multiple pathophysiological factors, from advanced glycation end-products to hemodynamic changes, are at play. TAS, despite showing stark intergroup differences, also did not emerge as a statistically significant predictor in the regression, possibly because overall antioxidant capacity is influenced by numerous factors—nutritional status, genetic predispositions, medications, and ongoing disease processes—that may confound its direct relationship with renal or glycemic indices.

Overall, these results reinforce the notion that diabetic nephropathy is deeply intertwined with chronic hyperglycemia, heightened inflammation, and an overload of oxidative stress, which together contribute to structural and functional changes in the kidney. The interplay between elevated inflammatory markers (IL-10, Fetuin-A, OxLDL, and Adiponectin) and drastically reduced Total Antioxidant Status underscores an environment where pro-inflammatory pathways are dominant and the body's compensatory mechanisms are unable to maintain redox balance. In addition, the significant elevation of creatinine and cystatin C alongside diminished eGFR highlights advanced kidney damage, while the profound microalbuminuria signals a further breakdown of glomerular integrity. The pronounced differences in glycemic indices between the two groups reinforce the role of extended periods of poor glycemic control in accelerating renal decline. Importantly, the limited explanatory power of the regression model indicates that while these markers may serve as useful indicators of disease severity, other clinical factors—such as hypertension, lipid abnormalities, duration of diabetes, and genetic susceptibility—likely converge to shape individual outcomes. Therapeutically, these insights support strategies targeting both metabolic optimization and the reduction of systemic inflammation, perhaps through combined interventions focusing on optimal glycemic management, blood pressure control, and anti-inflammatory or antioxidant therapies. Future investigations with larger sample sizes or longitudinal designs may clarify causal pathways and validate whether certain markers, individually or in combination, can improve the prognostic accuracy for diabetic nephropathy progression. Nevertheless, the current findings provide a compelling snapshot of how inflammatory and oxidative markers, together with robust metabolic and renal parameters, can differentiate diabetic nephropathy patients

from those without nephropathy and underscore the complexity of managing and predicting this formidable diabetes complication.

CONCLUSION

In conclusion, the findings of this study underscore the interplay between chronic hyperglycemia, heightened inflammation, and reduced antioxidant defense mechanisms in driving diabetic nephropathy. Patients with nephropathy exhibited marked elevations in inflammatory markers (IL-10, Fetuin-A, OxLDL, and Adiponectin), poorer glycemic control (FBS, PP2BS, and HbA1C), and significantly diminished renal function (creatinine, eGFR, microalbumin, and cystatin C). The pronounced reduction in Total Antioxidant Status further underscored the extensive oxidative stress burden. Although regression analysis did not identify a single biomarker as a definitive predictor of outcomes (eGFR or HbA1C), these results emphasize the multifactorial nature of diabetic nephropathy and highlight the need for holistic therapeutic strategies that address both glycemic optimization and inflammatory-oxidative dysregulation for more effective prevention and management of this debilitating complication.

REFERENCES

1. World Health Organization. Global report on diabetes. Geneva: WHO; 2016.
2. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels: IDF; 2019.
3. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol. 2017;12(12):2032-45.
4. Collins AJ, Foley RN, Gilbertson DT, Chen SC. The state of chronic kidney disease, ESRD, and morbidity and mortality in the first year of dialysis. Clin J Am Soc Nephrol. 2009;4 Suppl 1:S5-S11.
5. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA. 2011;305(24):2532-9.
6. Reutens AT. Epidemiology of diabetic kidney disease. Med Clin North Am. 2013;97(1):1-18.
7. Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products. Circulation. 2006;114(6):597-605.
8. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414(6865):813-20.
9. Tuttle KR. Back to the future: Glomerular hyperfiltration and the diabetic kidney. Diabetes. 2017;66(1):14-6.
10. MacIsaac RJ, Ekinci EI, Jerums G. Progressive diabetic nephropathy. How useful is microalbuminuria staging? Nat Rev Nephrol. 2014;10(6):305-14.
11. Navarro-González JF, Mora-Fernández C. The role of inflammatory cytokines in diabetic nephropathy. J Am Soc Nephrol. 2008;19(3):433-42.
12. Lim AK, Tesch GH. Inflammation in diabetic nephropathy. Mediators Inflamm. 2012;2012:146154.
13. Sifuentes-Franco S, Pacheco-Moisés FP, Rodriguez-Carrizalez AD, Miranda-Díaz AG. The role of oxidative stress, inflammation, and autophagy in diabetic nephropathy. Int J Endocrinol. 2018;2018:1875870.
14. Kwon H, Pessin JE. Adipokines mediate inflammation and insulin resistance. Front Endocrinol (Lausanne). 2013;4:71.
15. Holvoet P. Oxidized LDL and coronary heart disease. Acta Cardiol. 2004;59(5):479-84.
16. Ix JH, Shlipak MG, Brandenburg VM, Ali S, Ketteler M, Whooley MA. Association between human fetuin-A and the metabolic syndrome: data from the Heart and Soul Study. Circulation. 2006;113(14):1760-7.
17. Benzie IF. Evolution of dietary antioxidants. Comp Biochem Physiol A Mol Integr Physiol. 2003;136(1):113-26.
18. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. Int J Biomed Sci. 2008;4(2):89-96.

19. Ghiselli A, Serafini M, Natella F, Scaccini C. Total antioxidant capacity as a tool to assess redox status: critical view and experimental data. Free Radic Biol Med. 2000;29(11):1106-14.
20. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010;107(9):1058-70.
21. Lambers Heerspink HJ, Gansevoort RT. Albuminuria is an appropriate therapeutic target in patients with CKD: the pro view. Clin J Am Soc Nephrol. 2015;10(6):1079-88.
22. Porrini E, Ruggenenti P, Mogensen CE, Azevedo MJ, Benozzi L, Garay SD, et al. Non-proteinuric pathways in loss of renal function in diabetic nephropathy. Lancet Diabetes Endocrinol. 2015;3(5):382-92.
23. Sharma K. Obesity and diabetic kidney disease: role of oxidant stress and redox balance. Antioxid Redox Signal. 2016;25(4):208-16.
24. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021;44(Suppl 1):S111-S124.
25. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with T2DM. Lancet. 1998;352(9131):837-53.
26. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in T2DM with nephropathy. N Engl J Med. 2001;345(12):851-60.
27. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. Nat Rev Nephrol. 2021;17(5):319-34.
28. Packer M. Critical importance of in-hospital initiation of therapies with proven to reduce mortality in patients with chronic heart failure. JACC Heart Fail. 2019;7(7):615-7.
29. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in T2DM and nephropathy. N Engl J Med. 2019;380(24):2295-306.
30. Donate-Correa J, Mora-Fernández C, Navarro-González JF. Targeting inflammation in diabetic kidney disease: Early clinical trials. Expert Opin Investig Drugs. 2015;24(9):1055-67.
31. MacIsaac RJ, Jerums G, Ekinci EI. Processes in the progression of diabetic nephropathy. Nephrology (Carlton). 2014;19(4):141-3.
32. Schainuck LI, Striker GE, Cutler RE, Benditt EP. Structural-functional correlations in renal disease. II. The correlations. Hum Pathol. 1970;1(3):631-41.
33. Gohda T, Tomino Y. Novel biomarkers for the progression of diabetic nephropathy: Soluble TNF receptors, NGAL, and L-FABP. Ren Replace Ther. 2016;2:27.
34. Perkins BA, Ficociello LH, Ostrander BEP, Silva KH, Weinberg J, Warram JH, et al. Microalbuminuria and the risk for early progressive renal function decline in T1DM. J Am Soc Nephrol. 2007;18(4):1353-61.
35. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119-31.
36. Wada J, Makino H. Inflammation and the pathogenesis of diabetic nephropathy. Clin Sci (Lond). 2013;124(3):139-52.
37. Thongboonkerd V, Klein JB. Proteomic analysis of the urinary proteome. Adv Chronic Kidney Dis. 2005;12(1):103-12.
38. Maezawa Y, Takemoto M, Yokote K. Cell biology of diabetic nephropathy: roles of endothelial cells, tubulointerstitial cells and podocytes. J Diabetes Investig. 2015;6(1):3-15.
39. Yokoyama H, Haneda M, Kurokawa K, et al. Chronic kidney disease categories and renal-cardiovascular outcomes in T2DM without proteinuria. J Diabetes Complications. 2014;28(3):406-12.
40. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: A report from an ADA consensus conference. Diabetes Care. 2014;37(10):2864-83.

41. Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev. 2013;93(1):137-88.