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Original Article

GLYCATIVE AND LIPOXIDATIVE STRESS BIOMARKERS CORRELATION WITH ADVANCED DIABETIC NEPHROPATHY

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ABSTRACT

Diabetic nephropathy (DN) is the leading cause of end stage kidney disease (ESKD). Among the factors that contribute to DN are inflammation and hyperglycemia induced oxidative stress. This case-control study examined serum levels of OS biomarkers, advanced glycation end products (AGEs) and oxidized low-density lipoprotein (ox-LDL), in 60 stage five chronic kidney disease (CKD) patients versus 60 healthy controls.

The biochemical parameters that were assessed include, creatinine, urea, eGFR, Hba1c, fasting blood glucose, albumin, and electrolytes. DN patients exhibited loss of kidney function (eGFR: $< 15\text{mL/min}/1.73\text{m}^2$; creatinine: 6-10 mg/dL; urea: 140-170 mg/dL), poor glycemic control (Hba1c: 6-8%; fasting glucose: 310-390 mg/dL), and low calcium and albumin levels (calcium: 9 to 9.8 mg/dL; albumin: 3.1 to 3.9 g/dL) compared to healthy controls. Electrolytes (sodium, potassium, and chloride) showed no significant differences due to dialysis correction. DN patients exhibited AGEs serum levels ranging from 3000 to 3300 ng/mL ($p = 0.0009$) and ox-LDL levels ranging from 27 to 30 ng/mL ($p < 0.0001$), that were significantly elevated compared to healthy controls, confirmed heightened OS. The high AGE levels contribute to DN through the induction of basement membrane thickening, fibrosis and inflammation leading to further podocyte injury. While high Ox-LDL levels induce endothelial dysfunction and inflammation contributing to nephron loss. These findings implicate AGEs and ox-LDL as key contributors to DN progression through tissue damage, inflammation, and lipid peroxidation. Their significant elevation in advanced DN highlights their potential as predictive biomarkers and therapeutic targets in CKD.

Keywords: Diabetic nephropathy, Chronic kidney disease, Oxidative stress, Advanced glycation end products, ox-LDL.

1. INTRODUCTION

Diabetic nephropathy (DN) is among the most prevalent and severe consequences of diabetes mellitus (DM), constituting the major cause of end stage kidney disease (ESKD) globally, contributing significantly to both morbidity and mortality (Maggiore *et al*., 2017; Valencia & Florez, 2017). Approximately 50% of individuals with Type 2 Diabetes mellitus (T2DM) and nearly one-third of those with Type 1 Diabetes mellitus (T1DM) develop chronic kidney disease (CKD) over the course of their lives (Maggiore *et al*., 2017). Among patients with T2DM, DN is the third most frequent cause of mortality after cardiac disorders and malignancies (González-Pérez *et al*., 2021; Roumeliotis *et al*., 2021b)

The condition leads to end stage kidney disease ESKD due to persistent albuminuria and gradual reduction in glomerular filtration rate (GFR), and elevation of blood pressure (Mottl *et al*., 2022; Thipsawat, 2021). As GFR declines the risk of mortality and ESKD increases with marked elevation in albuminuria. Patients that are in advanced stages of CKD demonstrating GFR (< 30 mL/min/1.73 m2) have the highest risk across albuminuria categories (Hoogeveen, 2022). Many mediators and pathways contribute to DN development progression including, angiotensin II (Ang-II), oxidative stress (OS), and inflammatory processes (Donate-Correa *et al*., 2020; Yanowsky-Escatell *et al*., 2020).

Oxidative stress has emerged as a key player among the various metabolic and hemodynamic disturbances triggered by hyperglycemia in the progression of DN, because it acts both as a cause and consequence of renal damage. As a result of excessive ROS production, proteins, lipids, and deoxyribonucleic acid (DNA) undergo several persistent changes and modifications (Yaribeygi *et al*., 2019). Redox potential is commonly assessed by biomolecule-derived oxidation products that remain persistent for a longer time as compared to ROS (Di Meo & Venditti, 2020).

The oxidation of macromolecules causes the accumulation of certain products. For example, malondialdehyde (MDA), 4-hydroxynonenal (HNE), Thio barbituric acid-reactive substances (TBARs), and F2-isoprostanes are produced during lipid peroxidation. While nucleic acid oxidation results in 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 8-hydroxyguanosine (8-OHG) production. AGEs, advanced oxidation protein products (AOPPs), protein carbonyls, and methyl glyoxal (MGO) are formed during protein oxidation (Demirci-Çekiç *et al*., 2022; Sies *et al*., 2022; Sies, 2020). Among these oxidation products, AGEs are significantly important because of their dual role in causing kidney damage and sustaining OS. AGEs can cause loss of kidney function through increasing the

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synthesis of matrix metalloproteinases (Ma *et al*., 2023). In addition to AGEs, oxidized form of lipoproteins, specifically oxidized low density lipoprotein (Ox-LDL), contributes to the progression of DN by exacerbating oxidative injury and promoting inflammatory responses within the renal microvasculature. This study aimed to evaluate AGE and ox-LDL as potential biomarkers of DN and to determine their role in progression of the disease.

2. METHODS AND MATERIALS

Blood Specimens

This study involved 60 advanced diabetic nephropathy patients and 60 healthy individuals as control group. 5 ml of blood samples were collected at Erbil Teaching Hospital's laboratory in Erbil city via phlebotomy. Blood samples were obtained from patients and control between October 1, 2024, and February 1, 2025, using a case-control strategy. 2 ml of the venous blood samples were placed in an EDTA tube for Hba1c test, while 3 ml were placed in a gel tube for checking the kidney function markers, electrolyte balance, and the analysis of serum levels of (AGE & Ox-LDL) via ELISA test. The gel tubes obtained were left at room temperature around 10 to 20 minutes for the blood to clot, then centrifuged for 5 minutes at 7,000 rpm to obtain serum. After serum separation, part of the serum was used to measure some biochemical parameters including (Calcium, Albumin, Creatinine, Urea, Sodium, Potassium, Chloride, and Fasting glucose) and the remaining serum was poured into labelled Eppendorf tubes and immediately stored at -20 C°.

Patient Characteristics

This study involved the analysis of Erbil City's DN patient's data. 50% of participants were male and 50% were female. Most of the study population (67%) fell in the 60–75 years age category, while (25%) were between 50 to 60 years old and the remaining (8%) were between 30 to 50 years old. Most DN patients (63%) had an average body weight ranging from 70 to 100 Kg, while 14% weighed between 50 and 60 Kg and 23% between 100 and 120 Kg before dialysis. After dialysis sessions, patients lose about 1 to 4 kg of their initial body weight due to the removal of excess fluids. In terms of height, (60%) of the DN patients were between 150 and 170 cm, 28% between 170 and 190 cm, and 12% between 140 and 150 cm. All patients had Type 2 Diabetes mellitus and were at stage 5 CKD.

Biochemical Tests

The biochemical test performed included: Calcium, Creatinine, Albumin, Urea, eGFR, Random Blood Glucose, Hba1c, Sodium, Potassium, and Chloride. The Hba1c, Calcium, Creatinine, Albumin, Urea, and Random Blood Glucose levels were determined by COBAS Integra 400 Plus clinical chemistry analyzer (Roche Diagnostics, Switzerland) device. On the other hand, the sodium, potassium and chloride levels were measured by (Diamond Diagnostics SmartLyte® Plus Electrolyte Analyzer, USA) following the manufacturer's instructions. The eGFR was calculated via CKD-EPI 2021 equation that estimates the GFR based on the serum creatinine level The CKD-EPI 2021 equation is: eGFR = 142 × min (standardized Scr/K,1) $^{\alpha}$ * max (standardized Scr/K,1) $^{-1.200}$ * $0.9938^{\text{age in years}}$ * 1.012 [if female] where:

- Min (standardized Scr/K,1) = the minimum of Scr/K or 1
- Max (standardized Scr/K,1) = the maximum of Scr/K or 1
- Scr = serum creatinine in mg/dL
- K = 0.7 (females) or 0.9 (males)
- α = -0.241 (females) or -0.302 (males) (Inker *et al.*, 2021)

AGE and Ox-LDL Measurement

The ELISA kits from ELK Biotechnology company in China were used to measure human advanced glycation end products (AGE) and human oxidized LDL levels. AGE and Ox-LDL levels were measured from 88 serum samples (including 68 patients and 20 controls). The kit employed competitive inhibition enzyme immunoassay technique. Their AGE and Ox-LDL data were presented in ng/mL, and their concentrations were determined via ELISA reader (ELX800 Absorbance microplate BIOTEK, USA) where 450 nm was used to measure the absorption.

Statistical Analysis

The comparison between patients' and the control group's oxidative stress levels and biochemical parameters was done via an unpaired t-test statistical analysis. Several normality tests were performed for all the data. These included D'Agostino & Pearson Omnibus, Shapiro-Wilk, and KS normality tests. Mean and standard deviation (M±SD) were used to present the data. For the evaluation of statistical significance, 0.05 was employed as the significance level. All the statistical analyses were performed via the GraphPad Prism 9 program.

3. RESULTS

The results of the biochemical assays, and ELISA tests in advanced diabetic nephropathy patients were compared with control, and they are shown in the following sub-sections.

Biochemical test results

The results are demonstrated in Figures (1,2,3,4) and Table 1&2. Serum creatinine, urea, and estimated GFR levels are shown for both groups. Data were significantly altered in patients compared to controls ($p < 0.0001$). All the results were significant. HbA1c and random blood glucose levels were significantly elevated in patients compared with controls ($p < 0.0001$), as shown in Figure 2 & Table 1. Sodium, potassium, and chloride showed no statistically significant differences between patient and control groups ($p > 0.05$). As indicated in Figure 4 & Table 1.

ELISA Test Results

A significant elevation of AGE levels was observed in the patient group compared with controls ($p = 0.0009$), as shown in Figure 5(A) and Table 2. Oxidized LDL concentrations were significantly higher in patients with diabetic nephropathy than in controls ($p < 0.0001$), as shown in Figure 5(B) and Table 2.

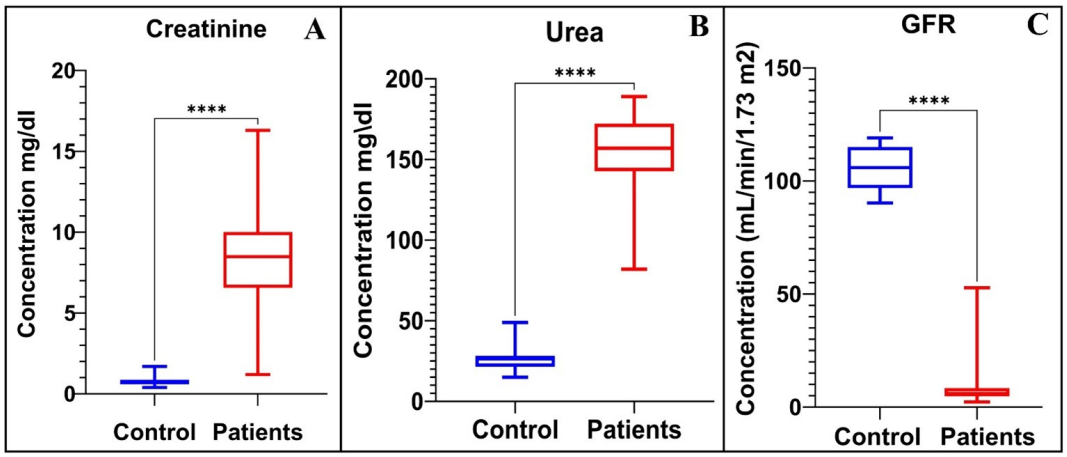

Figure 1: Kidney function test, A) Creatininee levels, B) Urea Levels, C) GFR Levels.

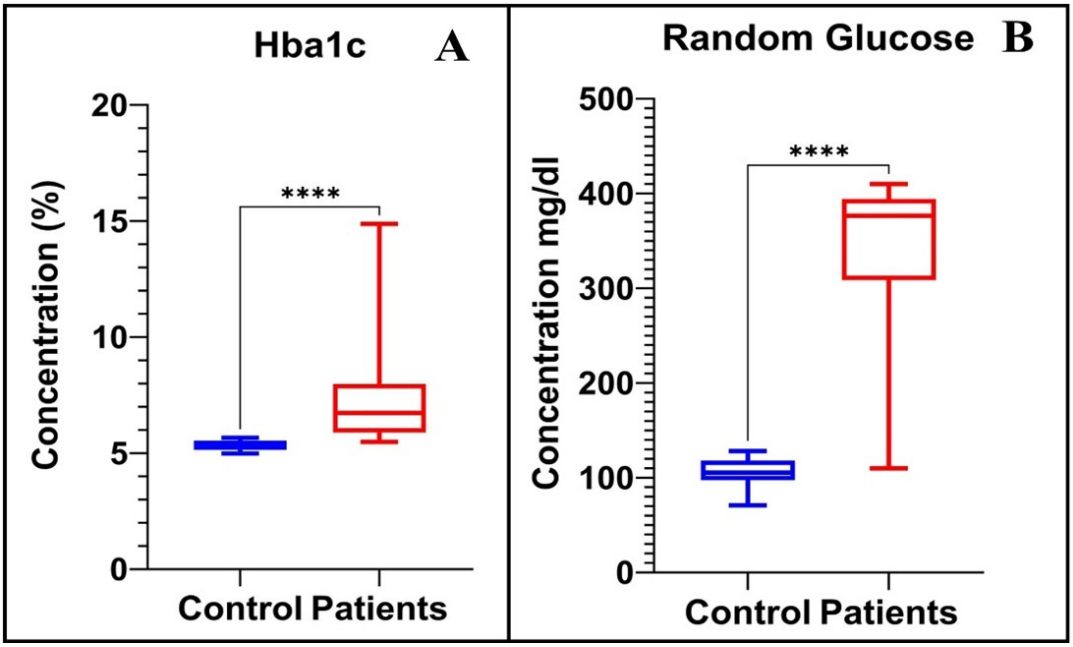

Figure 2: Glycemic control A) Hba1c levels, B) Random Glucose levels

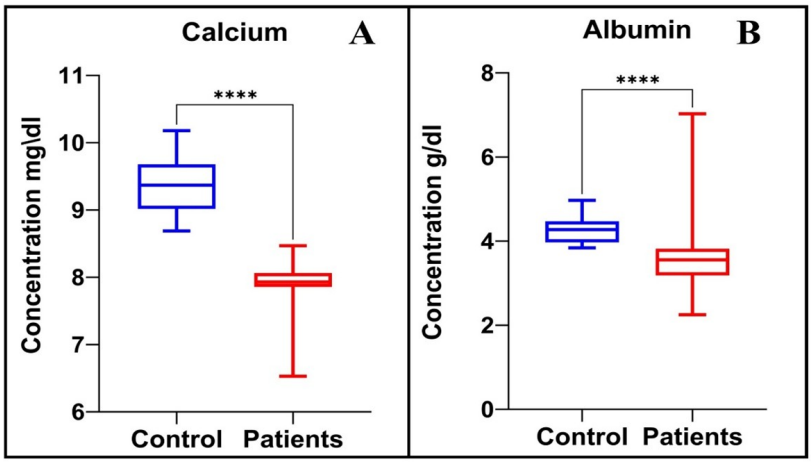

Figure 3: Electrolytes levels A) Calcium levels, B) Albumin levels.

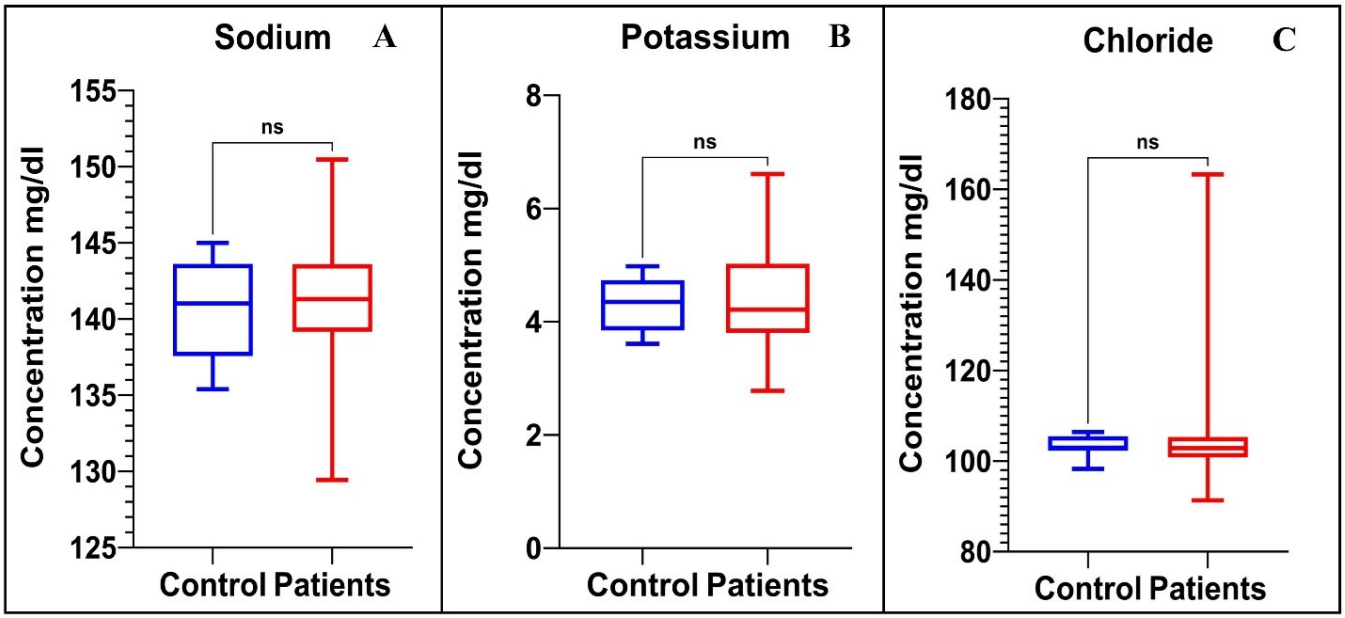

Figure 4: Electrolyte balance, A) Sodium, B) Potassium, C) Chloride.

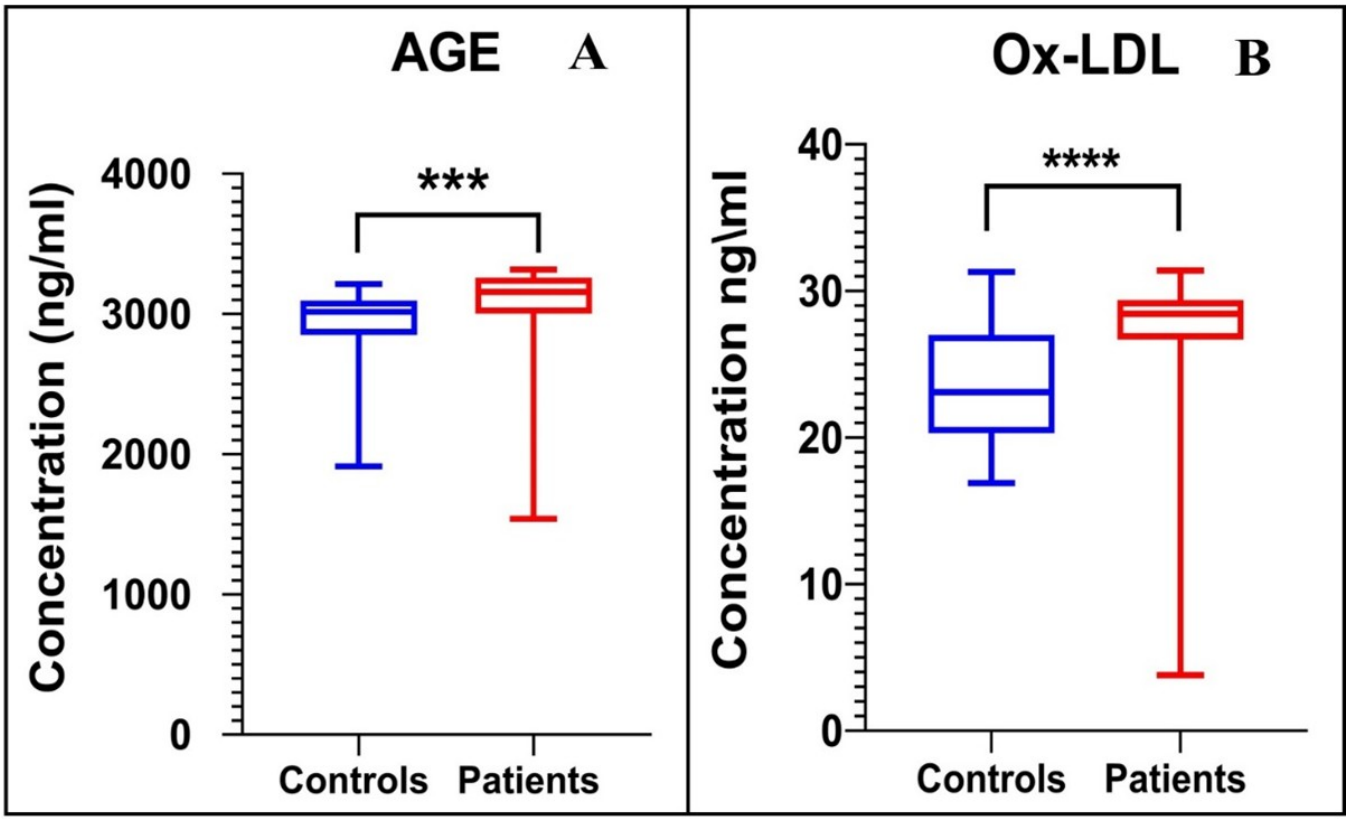

Figure 5: headingELISA test results, A) AGE levels, B) Ox-LDL levels.

4. DISCUSSION

DN is a leading cause of ESRD driven by persistent hyperglycemia and oxidative stress. Diverse factors including obesity, hypertension, and unhealthy lifestyle influence its development (Rossing, 2006). According to kidney function test results, the majority of patients in this study were classified as stage 5 CKD (GFR <15 mL/min/1.73 m2). This classification was identified based on GFR estimated via the CKD-EPI equation. The reduced GFR levels are indicative of progressive renal failure, accompanied by an imbalance in serum electrolytes and accumulation of metabolic waste products including creatinine and urea (Kumar *et al*., 2017). This finding was supported by the patient's results where the creatinine levels were within 6 to 10 mg/dl which was significantly higher than in healthy individuals and the urea levels were within 140 to 170 mg/dl in patients.

In addition to the reduced kidney function, metabolic imbalances were evident, particularly in glucose regulation. Biochemical re-

sults showed that DN patients had significantly elevated RBG and Hba1c levels, indicating poor glycemic control. Hyperglycemia has a key role in inducing endothelial damage by activating several damaging pathways, including (1) the activation of polyol pathway and metabolic pathways of glucose promoting glucose flow; (2) activation of the PKC isoforms, and hexosamine pathway ; (3) increase in intracellular AGE production and elevated expression of RAGE and ligands activation (Adeshara *et al*., 2024; Sifuentes-Franco *et al*., 2018). Therefore, it triggers glomerular damage, renal inflammation, and fibrosis contributing to reduction in kidney function, which was reflected in the rising creatinine, urea, albuminuria levels, and falling eGFR (Darenskaya *et al*., 2023).

Table 1: Statistical significance of the biochemical parameters

Biochemical Parameter	Patients (Mean ± SD)	Control (Mean ± SD)	p-value
Creatinine	8.495 ± 3.086	0.7567 ± 0.2327	<0.0001
Urea	153.9 ± 24.37	26.27 ± 8.124	<0.0001
GFR	7.580 ± 6.622	105.5 ± 9.454	<0.0001
HbA1c	7.224 ± 1.788	5.351 ± 0.1958	<0.0001
Random glucose	326.5 ± 105.4	106.5 ± 13.71	<0.0001
Calcium	7.925 ± 0.2536	9.366 ± 0.4136	<0.0001
Albumin	3.518 ± 0.6676	4.256 ± 0.3068	<0.0001
Sodium	141.1 ± 4.230	140.7 ± 3.148	0.6766
Potassium	4.442 ± 0.9163	4.327 ± 0.4501	0.9538
Chloride	103.8 ± 8.248	103.3 ± 2.208	0.5017

Table 2: Statistical significance of AGE and Ox-LDL

Parameter	Patients (Mean ± SD)	Control (Mean ± SD)	p-value
AGE	3082 ± 311.3	2921 ± 305.6	0.0009
Ox-LDL	27.50 ± 4.011	23.62 ± 4.075	<0.0001

Alongside the significant disturbance of glycemic control, serum electrolytes were evaluated. According to (Rao & Gb, 2022), the serum chloride and sodium levels are usually lower while the potassium is slightly higher in DN patients compared with healthy controls, though the values usually remain near the normal range. However, the electrolyte results indicated no significant difference between patients and control. This can be due to the continuous dialysis process that involved dialysate solutions which equalize patient's serum and standardizes these values. Research papers have shown the crucial role of oxidative stress in the progression of diabetic nephropathy, therefore, AGE and Ox- LDL levels were detected as OS biomarkers.

In this study, serum AGE concentrations were notably elevated in patients with DN (3000 ± 3300 ng/mL) compared to healthy controls (2800 ± 3000 ng/mL) which indicates increased glycation activity. AGES have a deleterious role in contributing to ESRD that has been discussed in several reviews (Mallipattu *et al*., 2012; Mallipattu & Uribarri, 2014). The accumulation of AGEs induces protein crosslinking and activates prooxidative and proinflammatory cellular signalling pathways therefore alters protein structure and function leading to tissue injury (Cheng *et al*., 2013). In contribution to oxidative stress, intracellular signalling and inflammatory responses activation are initiated through the adhesion of AGEs to RAGE or toll-like receptor 2 and 4 (Cheng *et al*., 2013).

A correlation was observed between AGE levels in renal tissue and DN. The balance between production and breakdown of extracellular matrix, including collagen and glomerular basement components was disrupted via AGE (Anil Kumar *et al*., 2014). AGE and collagen crosslinking inside the basement membrane contributes to the thickening of the membrane, impaired filtration, and gradually leads to glomerular function loss (Pasupulati *et al*., 2016). The AGE-RAGE axis is also crucial in DN.

Signals emitted by AGE-RAGE in tubular cells, podocytes, and mesangial cells stimulates TGF-β expression (Ott *et al*., 2014). JAK/STAT signalling pathway is responsible for TGF-β expression, which is a profibrotic factor promoting the synthesis of fibronectin, type IV collagen, and laminin therefore results in the thickening of the glomerular basement membrane. (Singh *et al*., 2014). AGEs and Rennin-Angiotensin Aldosterone System (RAAS) cross-linking is another mechanism that contributes to DN. Renin, angiotensin-converting enzyme (ACE), angiotensin I, and angiotensin II, play essential roles in regulating fluid balance as RAS components (Lin *et al*., 2018). When angiotensin II binds to angiotensin II type 1 receptor (AT1R) it leading to hypertrophy of mesangial and tubular epithelial cells. AGEs promote Angiotensin II activation through elevating AT1R expression (Parveen *et al*., 2021). Furthermore, AGE contributes to renal fibrosis and inflammation.

When RAGE is activated, various cytokines are expressed in kidney cells which in turn promotes the synthesis of monocyte chemoattractant protein-1 (MCP-1) that has a role in infiltrating macrophage and monocyte into the cell (Nowotny *et al*., 2015). Moreover, AGEs cause podocytopathy. Podocytes serve as a filtration barrier that controls the flow of plasma proteins from bloodstream to urine selectively depending on size (Pasupulati *et al*., 2016). Alongside the detrimental effects of AGEs, ox-LDL is another contributor in the progression of DN through amplifying oxidative injury and endothelial dysfunction.

OS enhances the buildup of free radicals as DKD worsens, resulting in reduced nitric oxide availability that is essential for vascular relaxation. In response, LDL particles in arterial walls will be oxidatively modified to Ox-LDL leading to the formation of the highly reactive lipid peroxide MDA (Roumeliotis *et al*., 2021a). In turn, MDA triggers the production of foam cells via the adhesion of macrophages and inflammatory cytokines to ox-LDL particles. Endothelial dysfunction is induced upon ox-LDL activation. This is a major indicator of atherosclerosis in T2DM and CKD patients (S. Roumeliotis *et al*., 2020). It has been shown in studies on CKD population that ox-LDL is one of the independent factors contributing to ED (Demir *et al*., 2010). In line with these findings, the results indicated an elevated levels of serum Ox-LDL in patients (27 ± 30 ng/mL) in comparison with control group (20 ± 27 ng/mL). The accumulation of lipid peroxides inside podocytes, mesangial, renal tubular, and renal epithelial cells leads to loss of nephron (Nosadini & Tonolo, 2011; Wu *et al*., 2021). Diabetic glomerulopathy develops as a result of continuous changes in the renal cells morphology and function via oxidative modifications (Gutwein *et al*., 2009). Glomerulosclerosis, fibrosis, and loss of kidney function arise from the accumulation of ox-LDL that is diet-derived which eventually leads to the reduction of eGFR by at least 30% (Duni *et al*., 2019; Liakopoulos *et al*., 2017).

Beside the findings highlight the potential of AGEs and ox-LDL as predictive biomarkers and therapeutic targets for monitoring and managing advanced DN, the study has several limitations that should be acknowledged. First, the sample size used for ELISA was unequal, because some samples were excluded for insufficient volume, which may lead to sampling bias. However, appropriate statistical methods were applied to reduce the likelihood of bias in results. Welch t-test was used for the data analysis of ELISA because it is specific for the comparison of groups with unequal variances for different sample sizes. Therefore, reliable results were obtained. However, an equal sample size would have further strengthened the statistical power.

Second, this study is a cross-sectional study where data was collected at a single time point. For future studies longitudinal monitoring of oxidative stress marker levels and biochemical markers is suggested at each stage of diabetic nephropathy to provide a better understanding of their role in the progression of the disease.

Third, the study is limited due to the lack of data regarding lifestyle factors such as, smoking, diet, and physical activity that would act as cofounding variables.

5. CONCLUSION

This study demonstrates significantly higher serum levels of OS biomarkers in DN patients than in healthy controls as reflected from AGEs levels (3000-3300 ng/mL vs. 2800-3000 ng/mL) and ox-LDL levels (27-30 vs.20-27 ng/mL), correlating with loss of kidney function (eGFR: <15mL/min/1.73m2) and poor glycemic control. These findings implicate AGEs and ox-LDL pathogenic role in progression of advanced DN through fibrosis, endothelial dysfunction, and inflammation. Therefore, both can serve as potential biomarkers for monitoring DN progression and as therapeutic targets in the future.

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Ethical Statment:

Ethical approval was obtained from the Human Ethics Committee of the Erbil Health & Medical Technical College, Erbil Polytechnic University (No. 25/0051 HRE), prior to the study.

Conflict of Interests:

The authors declare no competing interests.

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Author Contributions:

Corresponding author A. M S. has performed the practical section, data analysis of results, and manuscript writing, B. A. S., provided guidance and revised the final version of the manuscript.

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