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Estimation of Oxidative Stress and Inflammatory Markers Among Chronic Kidney Disease Patients in Libya

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تقدير مؤشرات الاجهاد التأكسدي والالتهاب لدى مرضى الكلي المزمن في ليبيا

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Abstract
The present work is designed to assess the impact of inflammatory and OS biomarkers on the development of CKD. This study included 30 control subjects and 70 CKD patients at stages 2-5, aged 20 to 75 years. Blood specimens were drawn from healthy individuals and patients to estimate kidney parameters, biomarkers of OS (ROS and TAC), and inflammation (IL-1β and CRP). An independent t-test was used for two-group comparisons, ANOVA for multiple comparisons, and Pearson's correlation coefficient for variable relationships. The study revealed progressive renal impairment, with a highly significant decrease (P = 0.000) in estimated Glomerular filtration rate (eGFR) across CKD stages. Conversely, serum levels of creatinine and urea were found to be markedly elevated (P = 0.000) in advanced stages compared to early stages and healthy subjects. Additionally, levels of Interleukin 1β (IL-1β) were considerably higher in the advanced stages compared to the early stage and healthy controls. Moreover, the reactive oxygen species (ROS) level was raised considerably (P = 0.03) in advanced stages compared to earlier stages; meanwhile, total antioxidant capacity (TAC) levels were lower in CKD patients and continued to decrease significantly (P = 0.000) in more advanced stages of the disease. Furthermore, ROS levels demonstrated a strong inverse association with eGFR, while showing a strong positive connection with creatinine and urea. In contrast, TAC exhibited a strong positive association with eGFR and negatively correlated with creatinine, urea, and uric acid. Additionally, CRP and IL1β levels were inversely related to eGFR and positively linked with creatinine and urea. Notably, ROS levels revealed a considerable positive association with both CRP and IL1β, while TAC displayed a significant negative correlation with these markers. Our findings demonstrated that inflammatory and OS biomarkers significantly increased in serum during the early stages of CKD. These results underscore their potential for facilitating early detection and improving strategies for prevention and diagnosis.

Keywords: Chronic Kidney Disease (CKD), Renal Function Parameters, Oxidative Stress (OS), Inflammatory Markers, IL-1β, Antioxidants.

الملخص
هدفت هذه الدراسة إلى تقييم تأثير المؤشرات الحيوية للالتهاب والإجهاد التأكسدي على تطور مرض الكلى المزمن. شملت الدراسة 30 شخصًا سليمًا و70 مريضًا بمرض الكلى المزمن في المراحل من 2 إلى 5، تتراوح أعمارهم بين 20 و75 عامًا. جُمعت عينات دم من الأفراد الأصحاء والمرضى لتقدير وظائف الكلى، والمؤشرات الحيوية للإجهاد التأكسدي (أنواع

الأكسجين التفاعلية(ROS) ومضادات الأكسدة الكلية (TAC)، والالتهاب (إنترلوكين-1 بيتا (IL-1β) وبروتين سي التفاعلي (CRP)). استُخدم اختبار t المستقل للمقارنات الثنائية، وتحليل التباين للمقارنات المتعددة، ومعامل ارتباط بيرسون للعلاقات بين المتغيرات. كشفت الدراسة عن تدهور تدريجي في وظائف الكلى، مع انخفاض كبير جدًا (P = 0.000) في معدل الترشيح الكبيبي المقدر (eGFR) عبر مراحل مرض الكلى المزمن. في المقابل، وُجد أن مستويات الكرياتينين واليوريا في الدم مرتفعة بشكل ملحوظ (P = 0.000) في المراحل المتقدمة مقارنةً بالمراحل المبكرة والأفراد الأصحاء. بالإضافة إلى ذلك، كانت مستويات IL-1βأعلى بشكل ملحوظ في المراحل المتقدمة مقارنةً بالمراحل المبكرة والأفراد الأصحاء. علاوة على ذلك، ارتفع مستوى ROS بشكل ملحوظ (P = 0.03) في المراحل المتقدمة مقارنةً بالمراحل المبكرة؛ في حين كانت مستويات TAC أقل لدى مرضى القصور الكلوي المزمن، واستمرت في الانخفاض بشكل ملحوظ (P = 0.000) في المراحل المتقدمة من المرض. كما أظهرت مستويات ROS ارتباطًا سلبيًا قويًا مع eGFR، وارتباطًا إيجابيًا قويًا مع الكرياتينين واليوريا. في المقابل، أظهرTAC ارتباطًا إيجابيًا قويًا مع eGFR، وارتباطًا سلبيًا مع الكرياتينين واليوريا. بالإضافة إلى ذلك، ارتبطت مستوياتCRP و IL-1β سلبًا مع eGFR، وارتباطًا إيجابيًا مع الكرياتينين واليوريا. والجدير بالذكر أن مستويات ROS أظهرت ارتباطًا إيجابيًا كبيرًا مع كل من ROS و IL-1β، بينما أظهر TAC ارتباطًا سلبيًا كبيرًا مع هذه المؤشرات. تُظهر نتائجنا ارتفاعًا ملحوظًا في مؤشرات الإجهاد التأكسدي والالتهاب في مصل الدم خلال المراحل المبكرة من مرض الكلى المزمن. وتُؤكد هذه النتائج على إمكانية استخدامها في الكشف المبكر وتحسين استراتيجيات الوقاية والتشخيص.

الكلمات المفتاحية: مرض الكلى المزمن، مؤشرات وظائف الكلى، الإجهاد التأكسدي، مؤشرات الالتهاب، الإنترلوكين1- بيتا، مضادات الأكسدة.

Introduction

Chronic kidney disease (CKD) is an important health problem in contemporary society and poses a considerable public health challenge, with its prevalence continuously on the rise [1]. It affects roughly 10% of the global population, and it is estimated that around 5 to 10 million individuals die from kidney disease each year worldwide [2]. Furthermore, in developing nations, the incidence about 15% higher than in developed countries [3]. In Libya, the regional distribution of kidney failure showed a prevalence of 16.1% in the East, 15.5% in the South, and 68.4% in the West, with males being more affected by ESRD than females across all three regions [4]. The most recent data indicated that kidney disease resulted in 1,186 deaths in Libya, accounting for 4.72% of total fatalities, which places Libya 66th in the world ranking [5].

CKD is characterized by a decline in renal structure, indicated by the presence of albuminuria, or a reduction in renal function, defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m², lasting for three months or longer [6]. CKD is classified according to KDIGO guidelines based on GFR stages (G1-G5) and albumin-to-creatinine ratio (A1-A3), with higher stages indicating more severe kidney dysfunction [7].

Reactive oxygen species (ROS) have important roles (functions in signaling and immunity; however, excessive levels of ROS can damage cellular structures, cause inflammation, and lead to tissue injury [8]. Under normal circumstances, the body's antioxidant system keeps ROS levels at safe levels. However, chronic disease or exposure to harmful substances can lead to oxidative stress (OS) [9]. This condition occurs when the levels of oxidants exceed those of antioxidants, resulting in cellular damage [8].

The kidneys are especially susceptible to the harmful effects of OS, as they have an extremely high level of metabolic activity and oxidative processes [9], making OS a major risk factor in CKD and ESRD. Therefore, OS is considered an important target for diagnosis and therapy [10]. Total Antioxidant Capacity (TAC) is an important measure of the body's overall antioxidant defense, indicating the combined effects of enzymatic and non-enzymatic antioxidants in neutralizing ROS and free radicals [11].

Interleukins (ILs) are a cluster of cytokines primarily produced by immune cells. They act as a crucial factor for controlling immune responses, mediating inflammation, and facilitating cell communication [12]. In cases of kidney disease, the activation of inflammasomes results in the release of interleukin-1 (IL-1) and interleukin-18 (IL-18). These ILs stimulate the production of interleukin-6 (IL-6), which in turn contributes to the production of C-reactive protein (CRP), further promoting inflammation [1,13, 14]

OS and inflammation both contribute to kidney injury by damaging vital molecular structures. This relationship is cyclical; the inflammation that arises to heal damage from free radicals can create more free radicals, leading to further injury to the renal tissue [15]. Early detection of CKD is crucial for preventing its progression and improving patient outcomes [16]. Conventional assessment such as serum creatinine and urea, often detect CKD only in its progressive stages. Therefore, there is a growing interest in identifying novel biomarkers that can facilitate earlier diagnosis and intervention [17].

Inflammatory markers such as IL-6, tumor necrosis factor-alpha (TNF-α) [18], and interleukin-1 beta (IL-1β) [9] indicate systemic inflammation, which is often elevated in patients with CKD and contributes to the progression of the disease. Additionally, markers of OS are important, as they significantly contribute to kidney injury. Evaluating these markers can help us better understand the pathophysiology of CKD and serve as tools

for intervention. [19, 20]. Therefore, the current study aimed to evaluate OS and inflammation indicators among chronic kidney patients in Libya and the potential of using these biomarkers as tools for the early diagnosis of CKD.

Material and methods

Ethical approval

The study was approved by the Ethical Committee of the University of Tripoli (Ref No. SREC/010/50). Informed consent was obtained from all participants before the study.

Study area and population

This study was carried out during the period between September 2023 and March 2024 on CKD patients who attended the nephrology outpatient clinic of the Tripoli hospitals (National Heart Center, Tajoura-Tripoli, Tripoli Central Hospital, and Tripoli Kidney Services Center). The population of this study consists of 100 participants of both males and females aged 20-75 years, 30 of them were healthy, and 70 of them had CKD (more than three months). The patients were classified into groups based on the stage of CKD (Estimated from the serum creatinine concentration) using the CG formula. Patients with acute kidney injury, malignancy, those who are undergoing treatment with antioxidant supplements and anti-inflammatory drugs, and patients on dialysis or who have had kidney transplantation were excluded.

Blood sample collection and processing

A sample of 5 ml venous blood was drawn from both groups (healthy and patients) and placed in special tubes free of any anticoagulant and left at laboratory temperature for 30 minutes. After blood clotting, a centrifugation process was performed for 10 minutes at a speed of 3000 rpm to obtain blood serum. The serum was stored at -80 ºC until the analysis of kidney function parameters, OS, and inflammatory biomarkers was performed.

Determination of kidney function parameters and CRP

Serum creatinine, urea, uric acid, and CRP levels were estimated using a spectrophotometry-based automated routine chemistry analyzer (Cobas Integra 400 plus, Germany) and were reported in mg/dL. Albumin concentration was measured using the Beckman Coulter AU 480 device and was read in g/dL.

Determination of TAC

TAC was measured in serum samples using a total antioxidant capacity assay kit, colorimetric, MAK187; Sigma-Aldrich, USA, according to the manufacturer's protocol. The principle of this assay is based on the reduction of cupric Cu^{2+} ion reagent to Cu+ by both small molecules and protein antioxidants, then the reduced Cu+ is chelated.

A 1 mM Trolox standard solution was prepared to create standard curve dilutions. In each well, 1 µl of each sample was mixed with 100 µl of ddH_2O before adding 100 µl of the Cu working solution. After incubating at room temperature for 90 minutes on an orbital shaker protected from light, a soluble purple color was developed, which was measured at 570 nm using a microplate reader. The amount of TAC of serum was estimated by comparing the measured OD values with the standard curve using the standard values of Trolox solution. The level of TAC in the specimens was calculated using the equation of the standard curve and expressed as nmol/µl.

Estimation levels of serum ROS (superoxide anion)

20 µl of serum was added to the dissolved Agarose N-Gel tube containing Nitro Blue Tetrazolium (NBT) and mixed gently. The tube was incubated for 55 minutes at 37 ºC. The color change was observed immediately and compared to the color code listed in the kit catalog to determine the level of ROS present in the sample. This test is based on the reduction of NBT dye to detect superoxide anion in the sample; it produces a color ranging from light pink to dark purple, level 0 to 3.

Determination of IL-1β

Human IL-1β was measured in serum samples using an enzyme-linked immunosorbent assay kit (ELISA kit), Colorimetric BMS224-2TEN; Invitrogen according to the manufacturer's protocol. The test is based on the binding of human IL-1β present in the sample or standard to antibodies that are adsorbed onto microwells. Initially, a biotin-conjugated antihuman IL-1β antibody is added, which binds to the human IL-1β already captured by the first antibody. After incubation, any unbound biotin-conjugated antihuman IL-1β antibody is removed during a washing step. Next, streptavidin-HRP is added, which binds to the biotin-conjugated anti-human IL-1β antibody. Following another incubation period, unbound streptavidin-HRP is removed during a wash step. A substrate solution that reacts with HRP is then added to the wells, resulting in the formation of a colored product that is proportional to the amount of human IL-1β present in the sample or standard. The reaction is terminated by the addition of acid, and the absorbance is measured at 450 nm.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 23 for Windows was used to analyze the data statistically. The Kolmogorov-Smirnov test was performed to assess normality. All variables in this study were normally distributed; therefore, parametric tests were used. A one-way analysis of variance (ANOVA) was applied to compare all parameters across multiple groups and identify significant differences, followed by a post hoc Tukey test to determine which means differ significantly. The independent t-test was used for comparisons between two groups. Pearson's correlation coefficient (r) was used to evaluate the relationship between variables. Statistical significance was set at a p-value < 0.05.

Results

The study included 100 participants, consisting of 70 patients and 30 healthy individuals. Among the patients were 40 males (57.1 %) and 30 females (42.9 %). The healthy group consisted of 10 males (33.3 %) and 20 females (66.7 %). The patients were categorized into four groups (S2-S5) based on their eGFR (ml/min/1.73 m^2). Group 1 (S2) with an eGFR of 60-89, Group 2 (S3) with an eGFR of 30-59, Group 3 (S4) with an eGFR of 15-29, and Group 4 (S5) with an eGFR of less than 15 ml/min/1.73m^2.

Comparison of kidney parameters, inflammatory and OS biomarkers between patients and healthy groups

The results showed a highly significant difference between the two study groups for all kidney function parameters, as shown in Table 1. The average eGFR values for CKD patients were notably lower than those of the healthy group, P = 0.000. Additionally, the mean values of creatinine, urea, and uric acid were considerably higher in the CKD patients compared to healthy individuals, P = 0.000. In contrast, a substantial decline in serum albumin was observed in the patients group P = 0.000.

Furthermore, serum IL-1β levels and CRP levels appeared statistically significant among the two groups with P values = 0.000 and 0.031, respectively. Additionally, the levels of ROS in CKD patients were considerably higher than healthy subjects, with a P-value of 0.000. Conversely, the TAC level in the CKD group was significantly lower compared to the healthy group, P = 0.000 as provided in Table 1.

Table 1. Comparison of kidney parameters, oxidative stress biomarkers and inflammatory biomarkers between healthy and patients.

Parameters	Healthy group	Patients	P-value
eGFR (ml/min/1.73m^2)	116.294±25.697	32.347±15.573	**0.000**
Creatinine (mg/dl)	0.7942±0.1659	3.190 ± 1.859	**0.000**
Urea (mg/dl)	22.645±4.923	93.743±44.229	**0.000**
Uric acid (mg/dl)	4.277±1.024	6.913±2.219	**0.000**
Albumin (g/dl)	4.923±0.511	4.403±0.6139	**0.000**
CRP (mg/dl)	1.2903±1.222	10.156±21.801	**0.031**
IL-1β (pg/ml)	5.285±1.0101	8.586±1.283	**0.000**
TAC (nmol/µl)	9.3296±0.933	3.686±1.303	**0.000**
ROS levels	0.1667±0.379	2.129±0.7003	**0.000**

Data are presented as mean ± SD, Abbreviations: eGFR: estimated Glomerular Filtration Rate; CRP: C-Reactive Protein; IL-1β: Interleukin-1Beta; TAC: Total Antioxidant Capacity; ROS: Reactive Oxygen Species.

Comparative analysis of kidney parameters, inflammatory and OS biomarkers between healthy individuals and patients at different stages of CKD

The average eGFR (ml/min/1.73m^2) declined progressively with increasing severity of kidney disease; it was highest in stage 2 when compared to stages 3, 4, and 5, P = 0.000, Table 2. The eGFR values in stage 2 were significantly lower compared to those of the control group, P < 0.05. Similarly, the eGFR in stage 3 showed a marked reduction compared to stage 2, P < 0.05 as shown in Table 3. On the other hand, mean creatinine (mg/dl) and urea levels (mg/dl) were lower in stage 2 compared to those in stages 3, 4, and 5 with a P-value of 0.000 as presented in Table 2. While levels of creatinine and urea in stage 2 did not show statistical significance when compared to the healthy group (P > 0.05). Also, no considerable variation was found between stages 2 and 3 for either biomarker (Table 3). However, there was no significant difference in the mean uric acid and albumin across the stages of CKD, P = 0.111, and 0.099, respectively.

Our findings regarding inflammatory biomarkers indicated that the concentration of IL-1β (pg/ml) significantly increased as the severity of CKD progressed in patients. Specifically, the IL-1β level was lower in stage 2 compared to stages 3, 4, and 5 (P = 0.000), Table 2. Interestingly, however, levels of IL-1β (pg/ml) were significantly lower in stage 2 than those in the control group, P < 0.05, as illustrated in Table 3.

Moreover, in terms of OS biomarkers, Table 2 shows a significant difference in the mean levels of ROS among different stages of CKD patients, with a statistical significance of P = 0.03. Notably, there is a considerable difference between healthy individuals and patients in stage 2 (Table 3). In contrast, TAC concentrations (nmol/µl) declined significantly as CKD advanced (P = 0.000). Interestingly, TAC levels of stage 2 patients differed significantly from those of the control group (P < 0.05). Similarly, TAC in stage 3 showed a marked reduction compared to stage 2, P < 0.05, as shown in Table 3.

Table. 2. Comparison of kidney parameters, oxidative stress biomarkers, and inflammatory biomarkers between different stages of CKD.

Parameters	Stage 2	Stage 3	Stage 4	Stage 5	P-value
eGFR (ml/min/1.73m^2)	74.223±2.259	41.9197±9.009	22.098±5.028	10.660±1.825	**0.000**
Creatinine (mg/dl)	1.463±0.3099	2.085±0.540	3.726±1.407	6.989±1.866	**0.000**
Urea (mg/dl)	40.400±9.374	72.392±27.243	108.456±32.293	159.081±65.044	**0.000**
Uric acid (mg/dl)	7.333±1.1504	7.187±2.129	6.189±2.201	8.231±2.478	0.111
Albumin (g/dl)	4.667±0.1155	4.558±0.524	4.341±0.654	4.000±0.6325	0.099
CRP (mg/dl)	2.410±0.531	5.382±7.975	15.702±33.101	14.587±7.867	0.265
IL-1β (pg/ml)	7.143±0.1617	7.672±0.6665	9.126±0.8512	10.517±1.291	**0.000**
TAC (nmol/µl)	6.890±1.006	4.189±0.998	2.979±0.5913	2.164±0.4357	**0.000**
ROS level	1.333±0.5774	2.000±0.7906	2.259±0.5257	2.571±0.5345	**0.03**

Significant p-values are indicated in bold**.** Data are presented as mean ± SD. Abbreviations: eGFR: estimated Glomerular Filtration Rate; CRP: C-Reactive Protein; IL-1β: Interleukin-1Beta; TAC: Total Antioxidant Capacity; ROS: Reactive Oxygen Species.

Table 3. Comparison of kidney parameters, oxidative stress and inflammatory biomarkers between healthy individuals and patients at stages 2 and 3 of CKD.

parameter	Healthy group	Stage 2	Stage 3	Stage 4
eGFR (ml/min/1.73m^2)	116.29±25.697	74.22±2.259*	41.919±9.009*#	22.098±5.028*#
Creatinine (mg/dl)	0.7942±0.1659	1.463±0.3099	2.085±0.540*	3.726±1.407*#
Urea (mg/dl)	22.645±4.923	40.400±9.374	72.392±27.243*	108.46±32.29*#
CRP (mg/dl)	1.2903±1.222	2.410±0.531	5.382±7.975	15.702±33.101*
IL-1β (pg/ml)	5.285±1.0101	7.143±0.1617*	7.672±0.6665*#	9.126±0.8512*#
TAC (nmol/µl)	9.3296±0.933	6.890±1.006*	4.189±0.998*#	2.979±0.5913*#
ROS levels	0.1667±0.379	1.333±0.5774*	2.000±0.7906*	2.259±0.5257*#

Data are presented as mean ± SD, * significantly differs from the healthy group (P < 0.05), # considerably differs from stage 2 (P < 0.05).

Association between biomarkers of inflammation, kidney function parameters, age, and BMI

CRP level was found to be negatively correlated with eGFR and albumin, while positively correlated with serum creatinine, urea, uric acid, and age. Furthermore, IL-1β levels were positively correlated with serum creatinine, urea, age (P = 0.000), and BMI (P = 0.003). Conversely, IL-1β was negatively correlated with eGFR (P = 0.000) and albumin (P = 0.022). However, the relationship between IL-1β and uric acid was not statistically significant, as shown in Table 4.

Table 4. Pearson correlations between inflammatory biomarkers, kidney parameters, age, and BMI**.**

Variables	Pearson correlations (r) and P-value	CRP (mg/dl)	IL-1β (pg/ml)
eGFR (ml/min/1.73m^2)	r P	**-0.229*** **0.022**	**-0.693**** **0.000**
Creatinine (mg/dl)	r P	0.159 0.114	**0.619**** **0.000**
Urea (mg/dl)	r P	**0.236*** **0.018**	**0.543**** **0.000**
Uric Acid (mg/dl)	r P	0.149 0.140	-0.202 0.052
Albumin (mg/dl)	r P	-0.186 0.064	**-0.237*** **0.022**
Age (years)	r P	**0.25*** **0.012**	**0.395**** **0.000**
BMI (Kg/m²)	r P	0.081 0.424	**0.303**** **0.003**

Significant p-values are indicated in bold**. **P<0.01, *P<0.05 are considered statistically significant.**
Abbreviations: eGFR: estimated Glomerular Filtration Rate; CRP: C Reactive Protein; IL-1β: Interlukin-1Beta; BMI: body mass index

Association between biomarkers of OS, kidney function, age and BMI

As indicated in Table 4, levels of ROS showed a negative correlation with both eGFR and serum albumin (P = 0.000). In contrast, ROS levels were positively correlated with serum creatinine, urea, uric acid, age (P = 0.000), and BMI (P=0.031). Moreover, TAC was positively correlated with eGFR (P = 0.000). On the other hand, statistically significant negative correlations were observed between TAC and creatinine (P = 0.003), urea (P = 0.000), and uric acid (P = 0.007). Additionally, TAC displayed a significant negative association with both age P = 0.002 and BMI P = 0.045, as shown in Table 4.

Table 5. Pearson correlations between oxidative stress biomarkers, kidney parameters, age, and BMI.

Variables	Pearson correlations (r) and P-value	ROS level	TAC (nmol/µl)
Creatinine (mg/dl)	r P	**0.623**** **0.000**	**-0.312**** **0.003**
Urea (mg/dl)	r P	**0.682**** **0.000**	**-0.473**** **0.000**
eGFR (ml/min/1.73m^2)	r P	**-0.817**** **0.000**	**0.720**** **0.000**
Uric acid (mg/dl)	r P	**0.537**** **0.000**	**-0.285**** **0.007**
Albumin (mg/dl)	r P	**-0.398**** **0.000**	0.200 0.062
Age (years)	r P	**0.515**** **0.000**	**-0.325**** **0.002**
BMI (Kg/m²)	r P	**0.216*** **0.031**	**-0.214*** **0.045**

Significant p-values are indicated in bold**. **P<0.01, *P<0.05 are considered statistically significant.**
Abbreviations: eGFR: estimated Glomerular Filtration Rate; TAC: Total Antioxidant Capacity; ROS: Reactive Oxygen Species; BMI: body mass index.

Association between OS and inflammatory biomarkers

Pearson's test revealed a significant association between biomarkers of OS and inflammation. Levels of ROS were positively related with CRP (P =0.001) and IL-1β (P = 0.000). Conversely, TAC levels displayed a negative association with CRP (P = 0.022) and IL-1β (P = 0.000), as shown in Table 6.

Table 6. Pearson correlations between oxidative stress biomarkers and inflammatory biomarkers**.**

Variables	Pearson correlations (r) and P-value	ROS level	TAC (nmol/µl)	CRP (mg/dl)	IL-1β (pg/ml)
ROS level	r P	-	**-0.680**** **0.000**	**0.326**** **0.001**	**0.600**** **0.000**
TAC (nmol/µl)	r P	**-0.680**** **0.000**	-	**-0.244*** **0.022**	**-0.833**** **0.000**
CRP (mg/dl)	r P	**0.326**** **0.001**	**-0.244*** **0.022**	-	**0.352**** **0.001**
IL-1β (pg/ml)	r P	**0.600**** **0.000**	**-0.833**** **0.000**	**0.352**** **0.001**	-

Significant p-values are indicated in bold**. **P<0.01, *P<0.05 are considered statistically significant.** Abbreviations: ROS: Reactive Oxygen Species; TAC: Total Antioxidant Capacity; CRP: C-Reactive Protein; IL-1β: Interleukin-1Beta.

Discussion

Kidney disease is a major public health issue worldwide because it is rarely diagnosed until its advanced stages. This delay is largely attributed to the absence of clinical symptoms in the early stages [19] and the fact that commonly measured renal function parameters, such as creatinine and urea, are only significantly altered when approximately 40-50% of the renal parenchyma is either reversibly or irreversibly damaged [21]. Consequently, this can lead to a lack of detection of the initial stages of CKD, delaying the diagnosis and appropriate therapeutic interventions [22].

Early diagnosis and management of CKD are essential to slowing disease progression and avoiding complications [23]. Therefore, over the past decade, various new renal biomarkers with higher sensitivity and specificity to renal disease have been created, facilitating the earlier detection of kidney damage compared to traditional methods [24].

The results of the current study provide important insights into the complex association between inflammation and OS, and the development of kidney disease among Libyan patients. Our findings demonstrate that the progression of CKD is linked to increased OS, reduced antioxidant defenses, and heightened inflammation.

Kidney function parameters in healthy individuals and patients

The outcomes of this study demonstrated that the eGFR in patients with CKD was markedly lower than that of the control group (Table 1). Additionally, there is a continuous progressive decline in GFR, a crucial clinical indicator of kidney function, as it decreases with the progression of CKD stages (Table 2). Conversely, the serum levels of creatinine, urea, and uric acid were significantly higher in CKD patients compared to healthy individuals (Table 1). These results are consistent with previous studies reporting a decrease in eGFR and increased levels of urea, creatinine, and uric acid in CKD patients [21, 25, 26]. On the other hand, a non-significant difference was observed in the levels of urea and creatinine between healthy subjects and patients at stage 2 of CKD (Table 3). This is consistent with previous research, which reported that serum creatinine and urea lack sensitivity in the early stages of CKD [27]. Furthermore, the levels of creatinine and urea significantly increased with advancing stages of CKD (Table 2). These outcomes are in accord with those reported by Dounousi et al. [28], who found that these parameters were markedly elevated with progression of CKD stages.

Inflammatory and OS indicators in healthy individuals and patients

The main pathological mechanism linking inflammation, OS, and the advancement of CKD involves initial damage to the kidneys caused by intracellular and extracellular oxygen-derived radicals, which subsequently leads to inflammation [29]. Both inflammation and OS contribute to kidney injury by damaging vital molecular components within the kidneys. Unfortunately, the relationship between inflammation and OS is cyclical. The inflammatory processes that occur to repair damage caused by free radicals can themselves become a source of additional free radicals, leading to further harm to renal tissue [15].

Inflammatory biomarkers in healthy individuals and patients

The results of the current study demonstrated a significant increase in inflammatory markers in patients with CKD compared to healthy individuals (Table 1), indicating a chronic inflammatory state associated with CKD. However, no substantial differences were observed in CRP levels across the different stages of the disease (Table 2), possibly due to high intra-group variability. Similarly, earlier studies (Adejumo et al., 2016; Gao et al., 2020) [30, 31], have reported that the CRP value was considerably higher in the CKD group in comparison to controls and was independently linked with faster rates of kidney function decline in CKD. Additionally, these results are consistent with those of Thaha et al. [32], who found no significant differences in serum hs-CRP levels between patients in stages 3, 4, and 5

Importantly, IL-1β exhibited a distinct pattern, showing substantially increased levels in patients with CKD relative to healthy individuals (Table 1). Notably, this elevation was also confirmed in stage 2 CKD cases relative to the healthy group, as provided in Table 3. This suggests that IL-1β may serve as a more sensitive marker for disease progression. Our findings are in agreement with the research conducted by [33], which revealed that IL-1β levels were considerably higher in CKD patients than in control subjects. Additionally, a gradual and significant increase in the level of IL-1β was detected across different stages of CKD (Table 2). These outcomes are aligned with the results of Prodhan et al. [34], who reported that IL-6 is strongly linked with the intensity of CKD than CRP.

McKnight et al. [35] demonstrated that IL-1β stimulates the production of fibroblast growth factor-23 (FGF-23), a hormone increasingly recognized as an early marker of kidney injury, indicating that IL-1β may act upstream in the early inflammatory pathway that triggers CKD. Additionally, neutralization of IL-1β in a mouse model has been found to suppress the expression of FGF-23 and alleviate early kidney injury, indicating its possible use as a diagnostic and therapeutic target. Also, a recent study revealed that inhibiting IL-1 could provide new therapeutic strategies for slowing the progression of CKD and reducing associated damage [36].

OS biomarkers in healthy individuals and patients

The results of the current study demonstrated a significant increase in ROS levels in patients with CKD when compared to healthy individuals (Table 1). Notably, a significant difference was found in this study between the control and patients in stage 2, as presented in Table 3. These findings indicate that systemic redox imbalance can be detected even in the early stages of CKD. Additionally, a progressive pattern in ROS levels was observed, correlating with the advancement of CKD stages (Table 2).

Our findings are compatible with the study of Kuchta et al. [37], who emphasized that OS markers were elevated in uremic patients compared to a control group, with these changes intensifying as eGFR declines, displaying significant differences among CKD stages [38]. The increase in OS is linked to the development of CKD, acting both as a cause and a consequence of the disease. Impaired mitochondrial function and increased ROS production have been identified as key contributors to elevated OS in CKD [19].

Mitochondria play a central role in generating ROS, but OS in CKD can also result from several other factors. These include aging, inflammation, uremic toxins, metabolic disturbances, and decreased antioxidant defense capacity, as previously mentioned [39, 40]. The present study demonstrated a significant decrease in TAC in patients with CKD compared to healthy individuals (Table 1). Additionally, a gradual decline in TAC was observed as the stages of CKD progressed (Table 2).

Although the levels of urea and creatinine showed no substantial variation between healthy individuals and patients at stage 2 of CKD, a notable disparity was found in ROS, TAC, and IL-1β, (Table 3), suggesting early oxidative and inflammatory alterations in CKD progression. Our results are consistent with previous studies [41, 42], which found that antioxidant levels were significantly reduced in patients with CKD compared to the control group.

The pathogenesis of CKD involves not only an increased generation of ROS but also a reduced efficiency of antioxidant systems [43]. Patients with CKD exhibit diminished antioxidant defense mechanisms, possibly due to decreased capacity for glutathione (GSH) scavenging [44]. Normally, both endogenous and dietary antioxidants protect cells against OS, inflammation, and damage. However, in CKD, these protective mechanisms are compromised. This may be due to multiple factors that contribute to the excessive production of ROS in CKD
patients, making effective control of ROS levels challenging [44].

Association of inflammation markers with renal parameters, age, and BMI

Patients with CKD often experience an elevated inflammatory state, and the systemic inflammatory response plays a crucial role in the progression of the disease. CRP, a well-known marker of inflammation, is typically found at increased levels in these patients [45]. Our results indicated a negative correlation between CRP levels and eGFR (Table 4), Previous studies support these findings, showing that CRP had a significant negative association with eGFR [46]. Additionally, another study confirmed that inflammatory markers like CRP, IL-6, and TNF-α are closely linked to decreased eGFR and increased albuminuria [47].

Moreover, in this study, CRP showed a significant positive correlation with age, while its correlation with BMI was insignificant. Previous studies have reported elevated CRP levels and reduced kidney function, particularly among older adults [48]. Contrary to our findings, other studies found a significant association between BMI and CRP levels in patients with CKD, highlighting the role of obesity in promoting systemic inflammation [49, 50].

Prior studies have reported that IL-1 can enhance the permeability of the glomerular filtration barrier to large molecules, an effect primarily through the production of ROS in response to this cytokine. Therefore, excessive IL-1 signaling may exacerbate proteinuria in certain pathological conditions [51, 36].

The findings of the current work reveal a strong negative correlation between IL-1β levels and eGFR (Table 4), suggesting a relationship between inflammation and declining renal function. These results align with earlier

research, which has demonstrated that elevated IL-1β is inversely associated with eGFR [45]. Additionally, a recent study found an association between reduced kidney function and elevated serum concentration of pro-inflammatory cytokines, including IL-1β, TNF-α, IL-6, as well as OS marker MDA [52].

Furthermore, our investigation established a strong positive association between IL-1β levels and both serum creatinine and urea (Table 4). These results are in agreement with other studies that have shown IL-1β levels positively correlated with creatinine and urea levels, suggesting that IL-1β levels could serve as a potential biomarker for renal injury [53, 54]. The strong negative correlation between IL-1β and eGFR, and the pronounced positive association with creatinine and urea, underscores that kidney impairment is closely related to the intensity of inflammation.

Regarding demographic factors, IL-1β was found to have a positive correlation with both age and BMI. This suggests that aging and increased body weight may be linked to higher levels of inflammatory markers. Previous studies on aged rats have shown an increase in IL-1β expression with advancing age [55]. Additionally, a study involving patients with CKD indicated that a higher BMI, particularly increased body fat mass, was significantly associated with elevated levels of IL-1β and other inflammatory markers [56].

Chronic systemic low-grade inflammation is a prevalent condition in CKD patients that plays a pivotal role in disease progression and development of related complications, particularly in those with advanced stages [57]. Notably, in the present study, a strong positive correlation was found between IL-1β and CRP (Table 6).

Prior investigation has revealed that the levels of IL-1β, IL-1RA, IL-6, TNF-α, and hsCRP in the serum are significantly elevated in patients with decreased eGFR. This elevation indicates an increased systemic inflammatory state that correlates with worsening kidney function. Notably, there is a positive correlation among different inflammatory markers, meaning that the elevation of one marker often coincides with increases in others; together, these markers contribute to the progression of CKD [58].

Association of OS markers with renal parameters, age and BMI

The kidney is a highly metabolic organ, abundant in oxidation reactions within its mitochondria, making it especially susceptible to damage from OS [59]. As a result, patients with CKD experience significantly higher levels of OS compared to healthy individuals, and these levels tend to increase as the eGFR declines [38]. The current study found a strong negative correlation between ROS levels and eGFR (Table 5). Consistent with previous research, an inverse association was noted between OS and eGFR among CKD patients, suggesting that higher OS is linked to greater renal dysfunction [60].

A recent study demonstrated a strong association between OS and impaired kidney function, indicating that increased OS correlates with elevated levels of creatinine, urea, and uric acid [61]. Consistent with these findings, the current study revealed significant positive correlations between ROS and each of the following markers: creatinine, urea, and uric acid (Table 5). Furthermore, an experimental study involving male rat models showed that both acute and CKI were associated with a marked increase in OS markers, alongside elevated levels of creatinine and urea [62]. This provides direct evidence of the crucial role OS plays in CKD progression.

A significant positive correlation was observed between ROS levels and both age and BMI in the present study. Our findings are consistent with studies conducted in humans [63], which confirmed that OS increases with aging and contributes to the progression of CKD. Other studies have also supported these results, showing a comparable association between higher BMI and increased OS levels [64, 65].

The results of a previous study indicated that habitual intake of a healthy diet is associated with a lower risk of CKD [66]. Supporting these findings, our study demonstrated a strong positive correlation between TAC and eGFR (Table 5), suggesting that better kidney function is associated with higher antioxidant capacity. Additionally, another study showed a positive association between oxidative balance score (OBS) and eGFR, indicating that higher OBS levels are associated with improved kidney function [67].

In our study, we found a significant inverse relationship between TAC and creatinine, urea, and uric acid (Table 5). These findings suggest that worsening kidney function is linked to a decrease in antioxidant defense. This aligns with earlier reports that showed a significant negative correlation between TAC and serum creatinine levels and a considerable positive association between TAC and eGFR [41, 68].

Our results revealed a significant negative correlation between TAC and age as well as between TAC and BMI (Table 5). These findings are consistent with earlier studies that indicated a substantial negative association between TAC and age, suggesting that antioxidant levels decline with advancing age [68]. In addition, Thiab et al. [69] demonstrated that advancing age leads to a marked reduction in the activity of key antioxidant enzymes in the rat kidney. This decline in enzymatic activity was further exacerbated under conditions of OS, highlighting the increased vulnerability of aging renal tissue to oxidative damage.

Similar to our findings, previous studies have reported a negative association between BMI and TAC in patients with CKD [65]. Additionally, a study conducted on overweight and obese patients with insulin resistance demonstrated that a higher BMI was associated with lower TAC and elevated OS markers [70].

Prior investigation has demonstrated that the progression of CKD is associated with increased markers of OS, such as MDA, and decreased levels of antioxidant enzymes, including SOD and GSH-PX. This imbalance indicates increased oxidative damage alongside reduced antioxidant defenses, contributing to a decline in kidney function [63]. In line with these findings, our study demonstrated a clear negative association between ROS and TAC (Table 6), reflecting the impact of OS on depleting antioxidant defense.

Correlation between inflammatory and OS indicators in CKD

Emerging evidence suggests that reducing OS and inflammation are two of the most effective approaches for slowing the progression of CKD [15]. Previous studies have shown that markers of OS and inflammation are significantly elevated in CKD patients compared to healthy individuals [63, 71]. In our current study, we found a significant positive association between levels of ROS and both CRP and IL-1β. Conversely, TAC displayed a substantial negative association with CRP and IL-1β (Table 6). Similarly, earlier research has established that pre-dialysis CKD patients exhibited significantly higher levels of MDA alongside increased IL-6 and hsCRP [72]. Furthermore, another study showed that the urinary ACR was positively correlated with IL-1β and TNF-α, as well as with MDA [52].

The interplay between OS and inflammatory markers offers insight into the pathophysiological processes by which OS leads to CKD. Elevated ROS generated during OS activates key inflammatory signaling pathways, notably through mediators such as NF-kB, resulting in increased levels of pro-inflammatory cytokines like IL-1β and CRP. In turn, these inflammatory mediators stimulate the activity of pro-oxidant enzymes, including NOX, thereby amplifying ROS production [10, 63]. This positive association between inflammation and OS suggests a synergistic interaction that may accelerate the progression of renal injury in CKD patients [72].

Conclusion

The results demonstrated a highly significant difference in OS and inflammatory biomarkers between healthy individuals and those with CKD. Additionally, these biomarkers demonstrated progressive changes across CKD stages, underscoring their association with disease advancement. Moreover, our results confirmed a significant association between inflammatory and OS markers and they play a crucial role in the development of CKD, as their levels increased significantly even in the early stages of the disease. Therefore, these significant findings highlight the diagnostic value of inflammatory and OS markers in the early detection of CKD. This suggests that incorporating these biomarkers into routine screening protocols among Libyan patients may enhance early diagnosis and facilitate timely therapeutic intervention.

Future research should adopt a complete and integrative approach to improve the early detection of CKD in Libyan patients. A major focus is the investigation of novel therapeutic interventions that target OS and inflammatory pathways, which are essential to CKD pathogenesis.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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