Biochemical variations in patients with renal failure: A comparative study

FAHAD D.F. ABO-GHNEIM[1], HUSSAIN JASEM MOHAMMED[2] and DHAFER A.F. AL-KOOFEE[3]

[1]Department of Medical Laboratory, Faculty of Healthy and Medical Techniques, Al-Furat Al-Awsat Technical University, Kufa, Najaf 54001, Iraq; [2]Department of Chemistry, Faculty of Science, University of Kufa, Kufa, Najaf 54001, Iraq; [3]Department of Clinical Laboratory Science, Faculty of Pharmacy, University of Kufa, Kufa, Najaf 54002, Iraq

Abstract. Chronic kidney disease (CKD) is a progressive condition characterized by declining kidney function, ranging from mild damage to end-stage renal disease. Its prevalence globally is estimated to be between 8 and 16%, with higher rates occurring in low- and middle-income regions. Underlying factors include diabetes, hypertension and genetic predisposition. The multifactorial nature of CKD is influenced by genetics, renal function monitoring, anemia, electrolyte imbalances and other risk factors. The present study collected 465 samples from subjects aged 18-65 years for a case-control study. These included 219 patients with CKD (101 females and 118 males; mean ages, 46.56 and 46.84 years, respectively) and 246 healthy individuals (131 women and 115 men; mean ages, 37.16 and 41.23 years, respectively). Whole blood was drawn for serum analysis for the purpose of comparing various biochemical parameters between patients with CKD and the healthy subjects, including total protein, albumin, ferritin, unsaturated iron binding capacity, iron, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, glucose, urea, serum creatinine, total calcium, free calcium, sodium, potassium, 8-hydroxy-2'-deoxyguanosine (8-OHdG) and phosphorus. The results obtained revealed a significant association between age and the occurrence of CKD (P<0.001), as well as between body mass index and the likelihood of developing CKD (P=0.031), indicating a connection between obesity and CKD. Biochemical analysis revealed disparities in several markers among patients with CKD, including glucose, urea, serum creatinine, iron, liver enzymes (ALP, AST and ALT), phosphorus, potassium, sodium, calcium and 8-OHdG (P<0.05). However, no notable differences in terms of sex were observed when comparing each sex group separately for the patients and controls. On the whole, the present study underscores the multifactorial nature of CKD, and its significant association with age. The 8-OHdG oxidative stress marker demonstrated potential in terms of distinguishing between CKD and healthy subjects. Further research is required, however, to explore additional CKD factors and to develop interventions for at-risk populations.

Introduction

Chronic kidney disease (CKD) is a condition characterized by kidney damage, leading to impaired blood filtration. Consequently, surplus fluid and waste accumulate in the body, potentially leading to additional health complications, such as stroke and heart disease (1). It affects between 8 and 16% of the global population, and is often overlooked by both patients and healthcare providers (2,3). It has been shown to be more common among low- and middle-income nations compared with high-income countries (4). CKD has long been predominantly linked to diabetes and hypertension worldwide. However, in regions, such as Asia, sub-Saharan Africa and a number of impoverished nations, additional factors, such as glomerulonephritis, infections and environmental exposures (including air pollution, herbal medicines and pesticides) are also prevalent causes (3). The development and progression of CKD are influenced by several factors, such as genetic, medical, lifestyle, metabolic, environmental and socioeconomic factors, and psychological factors affect the mechanisms through which CKD develops and progresses. The prevention of CKD and the attenuation of its course is greatly dependent on the early diagnosis and management of these risk factors (5). Genetic factors also play a crucial role in predicting CKD, particularly among individuals in which the condition progresses to end-stage renal disease (ESRD) (6). Furthermore, genetic predisposition may also contribute to increasing the risk of kidney failure (7,8).

Numerous factors can serve as crucial predictors of CKD, particularly in the case of individuals who develop hypertension (9). Hypertension is another key and primary cause of CKD, in addition to genetics and diabetes mellitus. CKD and hypertension often share common risk factors and influence each other, occasionally making it a challenge to distinguish between cause and effect (10).

Correspondence to: Dr Dhafer A.F. Al-Koofee, Department of Clinical Laboratory Science, Faculty of Pharmacy, University of Kufa, Street no. 40, Kufa, Najaf 54002, Iraq
E-mail: dhafera.faisal@uokufa.edu.iq

Carbohydrate intake affects insulin metabolism and general health, as diet plays a critical role in the management of CKD. Significant changes in insulin metabolism are linked to CKD and can be detrimental to the health of an individual. Rising blood levels of insulin in patients with CKD result from decreased insulin clearance caused by a deterioration in renal function. Insulin resistance has the potential to worsen metabolic disorders, such as diabetes by disrupting glucose homeostasis (11). Despite the wide fluctuations of exercise or food intake, the plasma glucose concentration in healthy individuals is 4-8 mM. This at most depends on the order of hormones that can precisely regulate the endogenous production of glucose. According to glucoregulatory factors, glucagon, insulin and catecholamines are critical acute glucoregulatory hormones and can modify the plasma glucose level in merely a few minutes. The glucose-lowering effects of insulin occur through membrane permeability to affect glycolytic enzymes to alter their effectiveness. Insulin facilitates glucose entry into cells by affecting membrane permeability (through GLUT4), its influence on glycolytic enzymes is more indirect. It occurs primarily through intracellular signaling pathways, rather than directly through changes in membrane permeability (12).

Monitoring kidney function requires both the determination of the urine albumin-creatinine ratio (uACR) and blood tests for blood urea nitrogen and creatinine, which assess the excretion of normal metabolic waste products via the kidneys and indicate decreased renal function, if present (13). The majority of reliable biomarkers and progression risk models for CKD prediction are serum creatinine and albuminuria (14). The glomerular filtration rate (GFR) is the most critical biochemical marker of kidney function. Regrettably, GFR cannot be estimated in the majority of clinical practices; therefore, it is based on filtration markers, such as serum creatinine. Another biochemical marker, albuminuria, may be a good indicator of reduced kidney function (15,16). There is still a widely acceptable degree of the concentration of creatinine required to qualify for a diagnosis of acute kidney injury (17).

Kidney disease affects the glucose threshold of the kidneys, with a low estimated GFR (eGFR) reducing the filtered glucose load, and the loss of functioning nephrons, reducing reabsorption capacity, consuming ~10% of plasma glucose (12). Both urine and blood tests provide a clear indication of the health status of the kidneys. Having an eGFR <60 ml/min/1.73 m^2 and/or an uACR >30 for ≥3 months is a sign of a kidney defect. Similarly, a level of albuminuria of at least 30 mg per 24 h, or signs of kidney damage, such as hematuria or structural abnormalities, also indicate a malfunction of the kidney (18).

Iron deficiency anemia is a common complication of CKD, characterized by absolute and functional iron deficiency, resulting from reduced iron stores and increased hepcidin levels (19,20). Individuals undergoing hemodialysis have a reduced production of erythropoietin due to iron loss via the hemodialysis device, as well as impaired iron absorption and transport from the gut to the circulation. The level of ferritin, unsaturated iron-binding protein capacity (UIBC), free iron form and the transferrin level are used for the purpose of verifying the iron status of a patient (21). CKD may result from oxidative stress, which plays a role in the deterioration of kidney function (22). 8-Hydroxy-2'-deoxyguanosine (8-OHdG) represents a common type of oxidative damage caused by reactive oxygen species, and is often employed as an indicator of oxidative stress (23). 8-OHdG is widely used as a DNA damage biomarker of systemic oxidative stress (24). 8-OHdG is one of numerous oxidative stress markers that can be used to predict renal function prognosis due to their excretion in urine (25). Elevated levels of 8-OHdG are associated with the development and progression of CKD due to increased inflammation, fibrosis and cell death in renal tissues. The regular monitoring of 8-OHdG levels in blood can help track the progression of CKD and the effectiveness of therapeutic interventions in an aim to lower oxidative stress and DNA damage by antioxidants and to potentially minimize the progression of CKD and improve overall kidney function (26). 8-OHdG itself is not a treatment target; therapies reducing oxidative stress can lower 8-OHdG levels and potentially attenuate the progression of CKD. It is commonly considered that oxidative stress hastens the deterioration of kidney function mechanistically (23).

Renal failure often leads to electrolyte imbalances, including hyperkalemia and dysnatremia, due to impaired renal fluid control, although the frequency of occurrence of dysmagnesemia remains uncertain (27). The blood levels of aspartate aminotransaminase (AST) and alanine amino transaminase (ALT) are both found to be markedly lower in patients with CKD with or without ESRD compared with healthy individuals (28). The decrease in albumin levels in patients with CKD is associated with a negative prognosis for kidney function and a deterioration in renal function, although this connection is yet not directly correlated, but rather becomes more pronounced when albumin levels decrease to <4.1 g/dl (29). Several risk factors, including serum electrolyte abnormalities, malnutrition (low albumin) and phosphorus imbalance, have been shown to be highly associated with CKD (30).

The kidneys play a vital role in preserving electrolyte homeostasis; electrolyte abnormalities are frequently observed in patients with CKD. Significant pathophysiological alterations and consequences result from the disruption of different electrolyte regulations caused by a loss or decline in renal function. Electrolyte abnormalities in CKD have key pathophysiological consequences and are linked to several difficulties, such as issues with the heart (cardiovascular, hypertension heart failure), bones (renal osteodystrophy, vascular calcification), muscles (weakness, lethargy) and metabolism (metabolic acidosis) (31). CKD increases the risk of developing cardiovascular diseases due to shared risk factors and CKD-induced conditions, such as hypertension, arterial stiffness and systemic inflammation. Impaired kidney function in CKD exacerbates cardiovascular risk through fluid overload and electrolyte imbalances (32).

Individuals with lower bilirubin concentrations have a greater risk of developing CKD. However, it remains uncertain whether high levels of total serum bilirubin (TSB) provide protection against mortality or raise the likelihood of requiring renal replacement therapy (33). Higher levels of ALP have been shown to be associated with a greater likelihood of developing ESRD and mortality from any cause in individuals with CKD at stage 3 or 4 (34). Finally, the adverse health consequences and increased mortality rates due to CKD may be associated with the type of anemia that is characterized by typically sized red blood cells and normal hemoglobin (Hb)

levels with diminished red blood cell production (35). The 8-OHdG biomarker has been found to be associated with a range of diseases, including diabetes mellitus and various neurovascular and cardiovascular diseases (36), although, to date, its association with CKD has not been extensively explored in the Arab population, and conflicting results have been obtained worldwide. Therefore, the aim of the present study was to investigate the association of 8-OHdG with the risk of developing CKD in patients in the Najaf/Iraq population. CKD has a significant and diverse socio-psychological cost that impacts social interactions, mental health, financial issues and general quality of life. The mitigating effects of CKD on the community can be improved awareness and offering sufficient resources (37). A potential strategy for CKD treatment care combines the measurement of established and new biomarkers with the most recent therapies. These biomarkers not only make it easier to identify and track the advancement of disease early on, but they also offer insightful information on how well-researched treatments are working based on focuses on slowing disease progression, managing complications and improving patient outcomes (38).

As regards the complexity of the interaction between CKD and cardiovascular disease, CKD induces a systemic, persistent proinflammatory state that plays a role in the remodeling of the heart and blood vessels. This leads to the development of atherosclerotic lesions, calcification and senescence of the blood vessels, cardiac fibrosis, and calcification of the heart valve (39).

Patients and methods

Study design, sample collection and measurements. The present study was a case series study comprising 465 samples collected from Al-Hakeem General Hospital and Al-Sadder Medical City l in Najaf, Iraq. The samples were classified into two categories: A total of 219 patients with CKD (including 101 females; average age, 46.56 years; and 118 males, average age, 46.84 years), and 246 healthy individuals (including 131 females; average age, 37.16 years; and 115 males, average age, 41.23 years). The participants and sample collection in the present study were in the age range of 18-65 years between January to May, 2023. Patients were diagnosed by specialized physicians with the use of the appropriate criteria for the diagnosis of patients with renal failure. The inclusion criteria were as follows: Patients who were clinically diagnosed with CKD (stage 4 and 5) and patients with an eGFR <15 ml/min/1.73 m². Subjects experiencing the following were excluded from the study: Participants <18 years of age, non-compliant persons, smokers, individuals with diabetes mellitus, hypertension, kidney transplant recipients, individuals with ischemic heart disease, patients with cancer and those receiving chemotherapy. The classic cardiovascular biomarkers were not assessed in the present study. Written informed consent was obtained from all patients and the healthy individuals that were used as a control group. The study protocol was approved by the Ethics Committee of the Facility of Medicine of the University of Kufa, under the document reference MEC-02.

Samples (5 ml) of whole blood were obtained from all patients with CKD and the control subjects. The serum was separated from the blood sample by centrifuging (25˚C) for 10 min at 10,000 x g. The total levels of the protein ferritin, UIBC, iron, albumin, ALP, ALT, AST, bilirubin, glucose, serum urea and creatinine were measured with using a fully automated biochemical analyzer (COBAS INTEGRA® 400 plus; Roche Diagnostics). Total calcium was estimated using an AVL 9180 Series Electrolyte Analyzer (Roche Diagnostics), whereas the levels/content of ionic calcium, sodium ion, potassium ion and phosphorus were measured using an ion-selective electrode method. To determine the body mass index (BMI), the height (in m) and weight (in kg) of each participant were measured according to the BMI formula (expressed in kg/m²) as follows: BMI (kg/m²)=weight/square of height in meters (m²).

Statistical analysis. The present study utilized IBM SPSS, version 26.0 software for Windows (IBM Corp.) for statistical analysis. The Kolmogorov-Smirnov test was employed to evaluate the distribution skewness of the variables under investigation. The variable data that skewed normal distributions are represented by the median values with the interquartile range (IQR). The Mann-Whitney U test was utilized to compare variables. Spearman's correlation analysis was conducted to explore the correlations between variables of interest. Receiver operating characteristic (ROC) curve analysis was employed to evaluate the sensitivity and specificity of 8-OHdG in the indicated groups as a detailed and robust assessment of its diagnostic performance, to determine the optimal threshold for clinical application, quantifying predictive power and facilitates comparisons with other biomarkers. The Mann-Whitney U test was utilized for the independent variables age, BMI, diabetes duration, fasting plasma glucose, HbA1c, serum creatinine, low-density lipoprotein (LDL)-cholesterol, iron, AST, ALT, ALP, total calcium, UIBC, total protein, albumin, ferritin, total bilirubin, phosphorus, calcium, sodium, potassium, Hb, packed cell volume test (PCV), white blood count (WBC), mean corpuscular volume (MCV), platelets and 8-OHdG to identify independent risk factors for the group. A value of P<0.05 was considered to indicate a statistically significant difference.

Results and Discussion

A comparison between patients with CKD and healthy individuals with respect to age and BMI was performed. Age and BMI may affect biomarker levels; thus, it was aimed to ensure that differences in the biomarker levels in patients with CKD and healthy individuals are not confounded by these variables. The levels of the biomarkers were tested between patients and healthy subjects following adjustment for age and BMI, so the covariates of the analysis of covariance (ANCOVA) model were applied. The results revealed statistically significant differences in biomarker levels between the groups following adjustment for age and BMI. The results indicated that the median age of the males in the control group was 42 years, with an IQR of 30-52 years, whereas for the group of patients, it was 46.75 years with an IQR of 41.75-54.25 years, indicating that a statistically significant difference existed between the ages of the males in the control and patient groups (P=0.003). As regards the females, the median age of the control group was 38 years with an IQR of 25-50 years, whereas for the female patients it was 46.72 years with an IQR of 39.5-52.5 years,

and the P-value determined was <0.001, likewise indicating a highly significant statistical difference between the ages of female controls and patients, as shown in Table I.

The findings of the present study were similar to those reported in the study by Al-Wahsh *et al* (40): Their study comprised 27,823 participants, and they found that 19% of the participants developed kidney failure and 51% did not survive, with the risk of kidney failure increasing with age. Those findings suggested an age-dependent effect for accurate risk prediction. The BMI values were also calculated in the present study, and these were found to have a significant effect in comparison with the healthy group, as reported in the study by Nguyen *et al* (41), in which Mendelian randomization analysis revealed that obesity did not serve as a separate cause of CKD, since dysglycemia and hypertension were implicated in the development of renal consequences, and they concluded that reaching or exceeding certain levels of weight loss decreases CKD outcomes. BMI is a crucial predictor in the development of CKD, with obesity playing a crucial significant role in kidney injury. Several studies have indicated a strong connection between an elevated BMI and the risk of developing CKD. Research in developed or emerging countries has demonstrated a close association between obesity and an increased risk of developing CKD. This risk also affects individuals with normal metabolisms, proving that in individuals without a metabolic illness, obesity alone is the cause of CKD (42). Both males and females with a high BMI are at a risk of developing CKD; however, the mechanisms and impact differ, and are often influenced by lifestyle, hormonal factors and socioeconomic status (43).

The results of the present study indicated substantial variations in biochemical and hematological parameters, when comparing the control subjects and patients, with the majority of the differences being statistically significant. The biochemical data of the enrolled patients and healthy subjects are presented in Table II. A significant difference in the glucose level was identified (P<0.001) for patients with CKD when compared with the control group. The kidneys maintain glucose homeostasis through the processes of filtration, reabsorption, consumption and generation. Glucose is filtered at the glomerulus and is reabsorbed in a healthy individual. Reabsorption occurs through sodium-glucose co-transporters, with a maximum rate of 375 mg/min. Glucose appears in urine as the plasma levels increase >200 mg/dl (12,44,45). The urea and creatinine levels were estimated in the present study, and significant increases were identified compared between the patients with CKD and the control individuals (P<0.001); this is due to an inability of the kidneys to clear creatinine during urine excretion, i.e., the function of kidney that results in increased levels of creatinine in the blood. The major end-product of protein catabolism is urea, which is produced via a series of reactions known as the urea cycle. As is well established, ammonia is converted into urea in the urea cycle, and this is subsequently transported via the blood to the kidneys for its removal from the body (46). The amounts of creatinine and urea in the blood of patients with CKD are assessed from the excretion of these compounds from the blood via the kidneys (47). The study by Pandya *et al* (48) revealed a significant [P=0.000 (<0.001)] correlation between the serum urea and creatinine concentrations in individuals with renal

disease. In the present study, the iron levels were found not to be affected by CKD, and an insignificant difference (P=0.301) was found after comparing the patients with CKD with the healthy individuals. However, individuals with chronic kidney failure were found to exhibit a slight, yet significant (P=0.001) decrease in Hb levels, which is a key indicator of the onset of anemia in conjunction with kidney failure. Anemia resulting from iron deficiency is a frequent consequence of CKD, characterized by a transferrin saturation index of ≤20% and a serum ferritin content of either ≤100 ng/ml (amount), or ≤200 ng/ml (i.e., concentration) or less (19,49). Herein, the liver enzymes (i.e., AST and ALT) were found to be associated with kidney failure through significant decreases in their levels and (P<0.001), and this finding was similar to that reported in the studies by Cavalcanti Sette *et al* (50) and Sabouri *et al* (51), which included patients with CKD undergoing hemodialysis who had decreased serum AST levels as a result of variables such as hemodilution, decreased pyridoxine levels and elevated homocysteine levels (50,51). The lower levels of liver enzymes in CKD are caused by factors, such as the withdrawal of aminotransferases, the resultant high lactate levels of which, through the dosages of relevant biomarkers (glucose, urea, serum creatinine, iron, ALP, AST, ALT, phosphorus, potassium, sodium, calcium and 8-OHdG), would rapidly expend nicotinamide adenine dinucleotide phosphate, other uremic factors that inhibit the activity of these enzymes, and the reduction of pyridoxine, a cofactor that is essential for the activity of aminotransferases (52,53). In patients with CKD, the present study identified that the levels of albumin and total protein were significantly decreased (P<0.001) compared with those of the healthy individuals. On the other hand, the ALP level was significantly increased in patients with CKD (P<0.001). Other than vascular calcification and arterial stiffness, other processes may contribute to the progression of CKD, and the overall mechanism that has been proposed comprises renal damage from arterial stiffness, highly pulsatile blood pressure and flow to the low-resistance renal vascular bed, defects in the filtration barrier leading to hyperfiltration and intraglomerular hypertension, eventually leading to nephrosclerosis. Several research groups have previously noted higher urinary protein excretion levels in those with higher ALP levels, and this contributes towards the progression of CKD (54-56). The present study is more similar to a previous study by Gatua *et al* (57), who included in their study the biomarkers total protein, albumin, AST, ALT, ALP and total bilirubin for patients with CKD. They found that patients with CKD had decreased levels of serum proteins, including albumin and total protein, whereas the levels of liver enzymes, including ALP, were higher. In addition, a decrease in AST and ALT levels were observed in patients with CKD, although the levels of bilirubin remained the same; the concentrations of phosphorus and potassium sodium ions in the present study were increased, whereas those of sodium ions and calcium were reduced, and all of these changes were found to be significant (P<0.001) when comparing the patients with CKD and the healthy subjects. These findings are in parallel with those in the study by Molla *et al* (58), who estimated the levels of serum electrolytes and performed a kidney function test. In the present study, the level of oxidative stress was detected by estimating the concentration of 8-OHdG, and

Table I. Median and interquartile values of the characteristics of the subjects in the present study according to age and sex.

	Males			Females		
Variable	Controls, median (IQR)	Patients, median (IQR)	P-value	Controls, median (IQR)	Patients, median (IQR)	P-value
Age (years)	42 (30-52)	46.75 (41.75-54.25)	0.003	38 (25-50)	46.72 (39.5-52.5)	**<0.001**
BMI (kg/m²)	24 (23-28)	22 (21-24)	<0.001	24 (21-28)	23 (22-24)	**0.031**

Values in bold font indicate statistically significant differences (P<0.05). BMI, body mass index.

Table II. Association between the significant values of biomarkers of patients with CKD and the control subjects.

Variable	Controls, median (IQR)	Patients, median (IQR)	P-value
Glucose (mg/dl)	105 (100-110)	121 (95-131)	**<0.001**
Creatinine (mg/dl)	0.73 (0.6-0.833)	10 (7.8-11.4)	**<0.001**
Urea (mg/dl)	24.2 (21.88-28.53)	156.21 (126-176)	**<0.001**
Iron (μg/dl)	89 (75.93-103)	83 (37-118.86)	0.301
UIBC (ug/dl)	212 (201-221.18)	206.5 (156-209.38)	**<0.001**
AST (u/l)	24.57 (19.6-27.7)	15.4 (10.3-21.56)	**<0.001**
ALT (u/l)	18 (13.68-24.25)	14.3 (8.9-22.81)	**<0.001**
T. bilirubin (mg/dl)	0.48 (0.3-0.58)	0.4 (0.22-0.5)	**<0.001**
T. protein (g/l)	8.44 (7.88-9)	5.93 (5.6-6.3)	**<0.001**
Albumin (g/dl)	4.8 (4.5-5.3)	3.9 (3.6-4.29)	**<0.001**
ALP (IU/l)	87 (80.9-92.25)	282.11 (201-311)	**<0.001**
Phosphorus (mg/dl)	5.33 (4.99-5.73)	5.84 (5.1-6.5)	**<0.001**
T. calcium (mg/dl)	9.4 (8.4-9.7)	8.8 (7.8-8.85)	**<0.001**
Ferritin (mg/dl)	85.5 (74.85-94)	476.95 (473-585)	**<0.001**
Potassium (mEq/l)	4.81 (4.5-4.99)	5.3 (5-5.5)	**<0.001**
Sodium (mEq/l)	136.33 (130-141.03)	120.59 (117-137)	**<0.001**
Calcium (mg/dl)	1.32 (1.27-1.39)	1.05 (1-1.1)	**<0.001**
Hb (g/dl)	13.39 (12-14.8)	10.2 (8.8-10.7)	**<0.001**
PCV (g/dl)	38.77 (37.98-40.43)	29.94 (26.3-33.5)	**<0.001**
WBC (g/dl)	8.47 (7.45-8.98)	6.33 (4.9-6.9)	**<0.001**
Platelets (g/dl)	280.6 (253.75-289)	162.97 (112-186)	**<0.001**
MCV (g/dl)	95 (91.63-96.24)	90.8 (90.66-91.26)	**<0.001**
8-OHdG (pg/ml)	174.58 (173.72-175.31)	417.8 (416.47-418.92)	**<0.001**

Values in bold font indicate statistically significant differences (P<0.05). IQR, interquartile range; CDK, chronic kidney disease; T., total; UIBC, unsaturated iron binding capacity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; Hb, hemoglobin; PCV, packed cell volume; WBC, white blood count; MCV, mean corpuscular volume; 8-OHdG, 8-hydroxy-2'-deoxyguanosine.

this was found to be increased in patients with renal failure compared with the healthy subjects (P<0.001). 8-OHdG, as well as 8-hydroxyl-2-deoxyguanosine, is a biomarker of DNA damage. The 8-OHdG levels in peripheral leukocyte DNA were found to be higher in patients with CKD compared with the control groups, as shown in Tables II and III. A decreased level of 8-OHdG in patients with CKD has been found to be associated with kidney creatinine clearance (59,60). By contrast, a higher plasma concentration of 8-OHdG has been independently connected with an increased risk of developing CKD, suggesting that this biomarker can be used to assess the progression of CKD. The results obtained for the levels of the 8-OHdG biomarker in the present study were found to be compatible with those of the study by Sanchez et al (61), i.e., that increased levels of 8-OHdG in the bloodstream were shown to be associated with a higher likelihood of developing renal disease.

In the present study, comparisons were made with the data obtained for various biochemical and hematological parameters in male and female patients with CKD. This analysis revealed significant differences in the various biochemical and hematological parameters when comparing the patients

Table III. Association of biomarker values according to sex in patients with CKD and healthy individuals.

	Males			Females		
Variable	CDK patientsmedian (IQR)	Control subjects median (IQR)	P-value	CDK patientsmedian (IQR)	Control subjects median (IQR)	P-value
Glucose (mg/dl)	121.42 (95-136)	105 (100-116)	**0.026**	121 (96-121.42)	105 (99-115)	**<0.001**
Creatinine (mg/dl)	10.16 (8.1-12.2)	0.75 (0.68-0.9)	**<0.001**	9.1 (7.3-10.9)	0.69 (0.56-0.78)	**<0.001**
Urea (mg/dl)	158.21 (126.25-186.5)	25 (22.7-28.5)	**<0.001**	156.21 (126-171)	23.38 (20.1-28.6)	**<0.001**
Iron (μg/dl)	68 (36.67-118.86)	90.4 (78.1-103)	**0.018**	109 (39.5-118.86)	87.4 (73.8-103)	0.309
UIBC (ug/dl)	206.73 (161.68-209.38)	209 (200-220)	**0.038**	206.5 (142.5-209.18)	214 (203-222)	**<0.001**
AST (u/l)	14.95 (9.45-21.56)	24.569 (19.5-28.1)	**<0.001**	16 (12-21.557)	24.569 (20-27)	**<0.001**
ALT (u/l)	14.25 (8.7-22.8)	18.1 (14.5-25)	**<0.001**	14.3 (9.3-22.8)	18 (12.2-24)	**0.021**
T. bilirubin (mg/dl)	0.4 (0.293-0.52)	0.5 (0.35-0.61)	**0.006**	0.4 (0.2-0.47)	0.43 (0.27-0.544)	**0.043**
T. protein (g/l)	5.93 (5.6-6.43)	8.44 (7.8-8.9)	**<0.001**	5.93 (5.45-6.2)	8.44 (7.9-9.1)	**<0.001**
Albumin (g/dl)	3.9 (3.5-4.1)	4.81 (4.6-5.5)	**<0.001**	3.9 (3.6-4.29)	4.8 (4.4-5.3)	**<0.001**
ALP (IU/l)	277 (182-311.75)	87.68 (83-95)	**<0.001**	283.11 (227.5-302)	85 (73.9-90.9)	**<0.001**
Phosphorus (mg/dl)	5.83 (5-6.725)	5.33 (4.8-5.6)	**<0.001**	5.83 (5.1-6.25)	5.33 (5.1-5.9)	**0.003**
T. calcium (mg/dl)	8.6 (7.79-8.85)	9.43 (8.78-9.7)	**<0.001**	8.85 (8-8.88)	9.3 (8.4-9.65)	**<0.001**
Ferritin (mg/dl)	476.95 (432.75-585)	85.5 (78-98)	**<0.001**	476.96 (476.95-585)	85.5 (58.1-87)	**<0.001**
Potassium (mEq/l)	5.3 (5.12-5.7)	4.81 (4.5-5)	**<0.001**	5.3 (4.7-5.33)	4.81 (4.5-4.99)	**<0.001**
Sodium (mEg/l)	136.59 (135-137)	136.33 (132-143)	0.501	136.59 (135-137)	136.33 (129-140)	0.497
Calcium (mg/dl)	1.05 (1-1.1)	1.32 (1.27-1.39)	**<0.001**	1.05 (1.01-1.1)	1.32 (1.28-1.39)	**<0.001**
Hb (g/dl)	9.9 (8.6-10.55)	14 (13-15.2)	**<0.001**	10.2 (8.85-10.7)	12.7 (11.8-15)	**<0.001**
PCV (g/dl)	29.94 (26.08-33.73)	39.89 (38.58-43.9)	**<0.001**	29.93 (26.8-33.25)	38.58 (36.7-39.8)	**<0.001**
WBC (g/dl)	6.3 (4.5-6.98)	8.66 (7.7-8.98)	**<0.001**	6.33 (5.15-6.65)	8.47 (7.3-8.98)	**<0.001**
Platelets (g/dl)	161.5 (106.5-195)	280 (253-285)	**<0.001**	162.97 (115-177.5)	280.6 (257-350.8)	**<0.001**
MCV (g/dl)	90.8 (90.7-91.26)	95 (92.4-96.84)	**<0.001**	90.8 (90.66-91.32)	93.99 (90.84-95.91)	**<0.001**
8-OHdG (pg/ml)	417.8 (416.47-419)	147.58 (173.1-175.31)	**<0.001**	417.8 (415.99-418.92)	174.58 (173.77-175.4)	**<0.001**

Values in bold font indicate statistically significant differences (P<0.05). IQR, interquartile range; CDK, chronic kidney disease; T., total; UIBC, unsaturated iron binding capacity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; Hb, hemoglobin; PCV, packed cell volume; WBC, white blood count; MCV, mean corpuscular volume; 8-OHdG, 8-hydroxy-2'-deoxyguanosine.

with the control subjects, with a majority of these exhibiting abnormalities in patients with CKD compared with the control group, as shown in Table III. These findings suggested the presence of underlying health conditions, such as metabolic disorders, renal dysfunction, liver injury, bone disorders, electrolyte imbalances and hematological abnormalities. No statistically significant differences were identified for iron or sodium when comparing the patients with the normal subjects, although it is important to note that even non-significant differences may still have clinical relevance.

Urea and creatinine are key biomarkers associated with kidney function, produced in the liver and muscle metabolism, filtered out of the blood by the kidneys, and excreted in the urine; this directly reflects their overall function. Uremia, cardiovascular complications, such as atherosclerosis, bone and mineral disorders such as calcium and phosphate imbalance, are some of the CKD-related complications associated with urea and creatinine (62). The association between liver function tests and CKD is multifaceted, reflecting the complex interplay between the liver and kidneys in maintaining overall metabolic homeostasis. Liver function tests are associated with some CKD-related complications, cardiovascular complications, and bone and mineral disorders (63). Hematological variables in the present study are associated with CKD through lowering erythropoietin production (64).

Further investigations and considerations in the context of the overall clinical picture are required in order to fully interpret these findings. Males are more prone to developing CKD than females due to decreased levels of high-density lipoprotein in males that participate in the growing cardiovascular complications and finally progress to CKD; this may be due to the activity of estrogen hormones in females within the reproductive period, but tends to diminish with age (65).

In the present study, correlation analysis for the various biochemical parameters was subsequently performed, and each cell in Table IV represents the Spearman's correlation coefficient between two variables and the corresponding P-value. This analysis provides insight into the associations between

Table IV. Correlation coefficients determined between the various biomarkers in patients with CKD.

		Glucose	Creatinine	Urea	Iron	UIBC	AST	ALT	T. Bill	T. Pr.	Alb.	ALP	Ph.	T. Ca.	Ferritin	K+	Na+	Ca+2	Hb	PCV	WBC	Plates	MCV	8-OHdG
Glucose	Rho	1.000																						
	P																							
Creatinine	Rho	0.127[b]	1.000																					
	P	0.006																						
Urea	Rho	.211[b]	.802[b]	1.000																				
	P	0.001	0.001																					
Iron	Rho	-0.002	-0.044	-0.066	1.000																			
	P	0.973	0.343	0.158																				
UIBC	Rho	-0.008	-0.159[b]	-0.181[b]	-0.040	1.000																		
	P	0.855	0.001	0.001	0.384																			
AST	Rho	-0.097[a]	-0.383[b]	-0.428[b]	0.155[b]	0.151[b]	1.000																	
	P	0.036	0.001	0.001	0.001	0.001																		
ALT	Rho	-0.035	-0.159[b]	-0.196[b]	0.236[b]	0.115[a]	0.642[b]	1.000																
	P	0.446	0.001	0.001	0.001	0.013	0.001																	
T. Bill	Rho	-0.195[b]	-0.085	-0.180[b]	0.155[b]	0.006	0.268[b]	0.259[b]	1.000															
	P	0.001	0.068	0.001	0.001	0.896	0.001	0.001																
T. Pr.	Rho	-0.139[b]	-0.679[b]	-0.679[b]	0.071	0.208[b]	0.458[b]	0.210[b]	0.134[b]	1.000														
	P	0.003	0.001	0.001	0.126	0.001	0.001	0.001	0.001															
Alb.	Rho	-0.119[a]	-0.562[b]	-0.565[b]	0.121[b]	0.143[b]	0.409[b]	0.268[b]	0.169[b]	0.689[b]	1.000													
	P	0.010	0.001	0.001	0.009	0.002	0.001	0.001	0.001	0.001														
ALP	Rho	0.130[b]	0.750[b]	0.729[b]	0.009	-0.154[b]	-0.323[b]	-0.057	-0.060	-0.629[b]	-0.516[b]	1.000												
	P	0.005	0.001	0.001	0.841	0.001	0.001	0.221	0.198	0.001	0.001													
Ph.	Rho	-0.006	0.256[b]	0.255[b]	0.001	-0.091	-0.010	0.008	0.081	-0.122[b]	-0.098[a]	0.212[b]	1.000											
	P	0.900	0.001	0.001	0.999	0.050	0.836	0.856	0.081	0.009	0.034	0.001												
T. Ca.	Rho	0.047	-0.306[b]	-0.215[b]	0.044	-0.001	0.093[a]	0.081	-0.068	0.296[b]	0.326[b]	-0.324[b]	-0.089	1.000										
	P	0.316	0.001	0.001	0.348	0.975	0.045	0.082	0.142	0.001	0.001	0.001	0.056											
Ferritin	Rho	0.090	0.740[b]	0.696[b]	0.060	-0.215[b]	-0.389[b]	-0.134[b]	-0.052	-0.689[b]	-0.603[b]	0.757[b]	0.215[b]	-0.280[b]	1.000									
	P	0.052	0.001	0.001	0.199	0.001	0.001	0.004	0.261	0.001	0.001	0.001	0.001	0.001										
K+	Rho	-0.003	0.379[b]	0.354[b]	0.008	-0.021	-0.142[b]	-0.053	0.075	-0.327[b]	-0.327[b]	0.331[b]	0.212[b]	-0.208[b]	0.371[b]	1.000								
	P	0.952	0.001	0.001	0.860	0.650	0.002	0.253	0.106	0.001	0.001	0.001	0.001	0.001	0.001									
Na+	Rho	-0.002	-0.019	-0.009	0.117[a]	0.021	-0.056	-0.016	0.032	-0.070	0.002	-0.023	0.032	0.074	0.027	0.145[b]	1.000							
	P	0.967	0.682	0.843	0.012	0.648	0.230	0.738	0.493	0.130	0.970	0.620	0.488	0.109	0.557	0.002								
Ca+2	Rho	-0.174[b]	-0.685[b]	-0.698[b]	0.058	0.145[b]	0.389[b]	0.210[b]	0.134[b]	0.626[b]	0.625[b]	-0.633[b]	-0.225[b]	0.442[b]	-0.660[b]	-0.378[b]	0.015	1.000						
	P	0.001	0.001	0.001	0.215	0.002	0.001	0.001	0.004	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.741							
Hb	Rho	-0.122[b]	-0.575[b]	-0.576[b]	0.001	0.093[a]	0.336[b]	0.128[b]	0.103[a]	0.571[b]	0.583[b]	-0.578[b]	-0.110[b]	0.239[b]	-0.605[b]	-0.250[b]	0.012	0.509[b]	1.000					
	P	0.009	0.001	0.001	0.977	0.045	0.001	0.006	0.027	0.001	0.001	0.001	0.017	0.001	0.001	0.001	0.798	0.001						

Table IV. Continued.

		Glucose	Creatinine	Urea	Iron	UIBC	AST	ALT	T. Bill	T. Pr.	Alb.	ALP	Ph.	T. Ca.	Ferritin	K⁺	Na⁺	Ca⁺²	Hb	PCV	WBC	Plates	MCV	8-OHdG
PCV	Rho	-0.165[b]	-0.553[b]	-0.593[b]	-0.053	0.092[a]	0.339[b]	0.158[b]	0.113[a]	0.556[b]	0.538[b]	-0.601[b]	-0.123[b]	0.224[b]	-0.604[b]	-0.288[b]	0.021	0.538[b]	0.884[b]	1.000				
	P	**0.001**	**0.001**	**0.001**	*0.250*	**0.047**	**0.001**	**0.001**	**0.015**	**0.001**	**0.001**	**0.001**	**0.008**	**0.001**	**0.001**	**0.001**	*0.654*	**0.001**	**0.001**					
WBC	Rho	-0.053	-0.507[b]	-0.452[b]	0.034	0.114[a]	0.184[b]	0.040	0.001	0.411[b]	0.325[b]	-0.498[b]	-0.150[b]	0.216[b]	-0.492[b]	-0.179[b]	-0.034	0.422[b]	0.292[b]	0.273[b]	1.000			
	P	*0.258*	**0.001**	**0.001**	*0.464*	**0.014**	**0.001**	*0.390*	*0.979*	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**	*0.470*	**0.001**	**0.001**	**0.001**				
Plat.	Rho	-0.085	-0.683[b]	-0.604[b]	-0.010	0.180[b]	0.288[b]	0.128[b]	0.061	0.555[b]	0.467[b]	-0.613[b]	-0.183[b]	0.227[b]	-0.604[b]	-0.289[b]	-0.007	0.573[b]	0.424[b]	0.420[b]	0.621[b]	1.000		
	P	*0.069*	**0.001**	**0.001**	*0.824*	**0.001**	**0.001**	**0.006**	*0.188*	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**	*0.882*	**0.001**	**0.001**	**0.001**	**0.001**			
MCV	Rho	-0.130[b]	-0.393[b]	-0.412[b]	-0.023	0.134[b]	0.180[b]	0.107[a]	0.200[b]	0.396[b]	0.368[b]	-0.365[b]	-0.109[a]	0.162[b]	-0.359[b]	-0.070	0.028	0.340[b]	0.411[b]	0.357[b]	0.181[b]	0.288[b]	1.000	
	P	**0.005**	**0.001**	**0.001**	*0.621*	**0.001**	**0.001**	**0.021**	**0.001**	**0.001**	**0.001**	**0.001**	**0.019**	**0.001**	**0.001**	*0.133*	*0.543*	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**		
8-OHdG	Rho	0.188[b]	0.632[b]	0.599[b]	0.031	-0.146[b]	-0.394[b]	-0.181[b]	-0.087	-0.550[b]	-0.482[b]	0.607[b]	0.117[b]	-0.170[b]	0.617[b]	0.276[b]	0.028	-0.583[b]	-0.546[b]	-0.597[b]	-0.336[b]	-0.457[b]	-0.360[b]	1.000
	P	**0.001**	**0.001**	**0.001**	*0.505*	**0.002**	**0.001**	**0.001**	*0.060*	**0.001**	**0.001**	**0.001**	**0.012**	**0.001**	**0.001**	**0.001**	*0.541*	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**	**0.001**

Values in bold font indicate statistically significant differences; values in italic font indicate no significant difference; [a]correlation is significant at 0.05; [b]correlation is significant at 0.01. CDK, chronic kidney disease; T., total; UIBC, unsaturated iron binding capacity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; T. Bill, total bilirubin; T. Pr., total protein; Ph., phosphorus; T.Ca., total calcium; K⁺, potassium; Na⁺, sodium; Hb, hemoglobin; PCV, packed cell volume; WBC, white blood count; Plat., platelets; MCV, mean corpuscular volume; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; P, P-value.
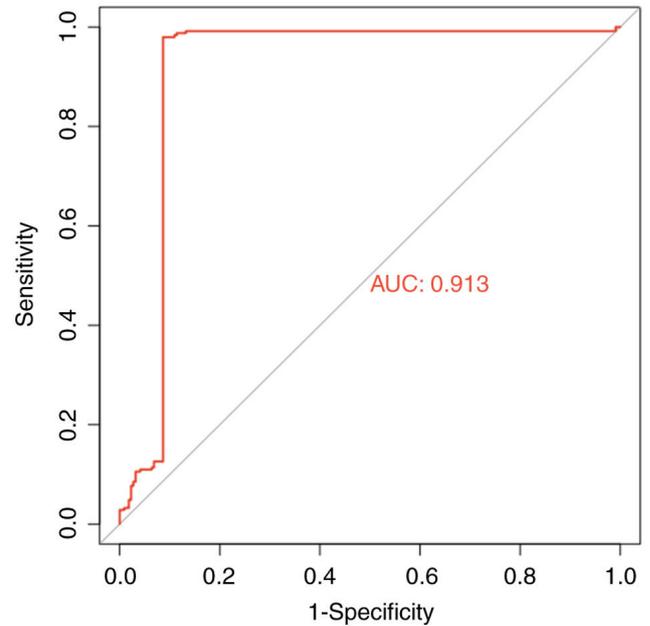

Figure 1. Area under the ROC curve analysis of the 8-OHdG biomarker for CKD detection. AUC, area under the curve; ROC, receiver operating characteristic; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; CKD, chronic kidney disease.

various biochemical parameters, which may be valuable for the understanding of the underlying physiological processes and the associated potential health conditions.

Positive correlations were identified for glucose with urea, total albumin, ALP, ferritin, potassium, calcium, Hb, PCV, WBC, total platelets. MCV and 8-OHdG. Positive correlations were identified for urea with total protein, albumin, ALP, ferritin, potassium, calcium, Hb, PCV, WBC, total platelets, MCV and 8-OHdG. A positive correlation was identified for creatinine with urea. Positive correlations were identified for total protein with albumin, ALP, ferritin, potassium, calcium, Hb, PCV, WBC, total platelets, MCV and 8-OHdG. Positive correlations were identified for albumin with ALP, ferritin, potassium, calcium, Hb, PCV, WBC, total platelets, MCV and 8-OHdG. Positive correlations were identified for ALP with ferritin, potassium, calcium, Hb, PCV, WBC, total platelets, MCV and 8-OHdG. Positive correlations were identified for ferritin with potassium, calcium, Hb, PCV, WBC, total platelets, MCV and 8-OHdG. Positive correlations were identified for potassium with calcium, Hb, PCV, WBC, total platelets, MCV and 8-OHdG. Positive correlations were identified for sodium with AST, TSB and total calcium. A positive correlation was identified for calcium with total calcium. Positive correlations were identified for Hb with PCV, WBC, total platelets, MCV and 8-OHdG. Positive correlations were identified for PCV with WBC, total platelets, MCV and 8-OHdG. Positive correlations were identified for WBC with total platelets, MCV and 8-OHdG. Positive correlations were identified for total platelets with MCV and 8-OHdG. Finally, a positive correlation was identified for MCV with 8-OHdG. In terms of negative correlations, these were identified for TSB with total protein and total calcium; total calcium was negatively correlated with TSB; Hb was negatively correlated with iron; and iron was negatively correlated with UIBC. On the other

hand, no significant correlations were identified for glucose, iron, UIBC, AST, ALT, phosphorus, sodium and 8-OHdG with the majority of the other variables.

The area under the ROC curve (AUC) values, ranging from 0 to 1, was evaluated to assess the discriminatory power of the model, with higher scores indicating superior performance. The AUC score that was obtained of 0.913, suggested that the model effectively discriminated between patients with CKD and normal individuals using the biomarker values for 8-OHdG. Therefore, this high AUC value indicated the robust capability of the model to distinguish between cases of CKD and non-CKD based on biomarker measurements, as illustrated in Fig. 1. The recent advancements in therapies, such as SGLT2 Inhibitors and gene therapy, and regenerative medicine can reduce oxidative stress lower 8-OHdG levels, and improve disease outcome. Finally, the studied biomarkers (liver function tests, renal function test, hematological assessment, and electrolytes) collectively provide a comprehensive picture of the physiological and biochemical disturbances in CKD, helping in the early detection, management, and prevention of CKD-related complications.

In conclusion, the results of the present study have revealed a significant association between age and the occurrence of CKD, highlighting the importance of age as a risk factor for the disease. Additionally, the present study has underscored the substantial impact of BMI on CKD development, indicating a close correlation between obesity and the risk of developing CKD.

The biochemical analyses revealed significant differences in several parameters, including glucose, urea, serum creatinine, iron, liver enzymes, aminotransaminases, phosphorus, potassium, sodium, calcium, and the oxidative stress marker 8-OHdG among individuals with CKD compared with healthy controls. However, the sex of the subjects did not reveal any notable differences in terms of the biomarkers evaluated in the present study when comparing each sex group separately for the patients and controls.

Availability of data and materials

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

Authors' contributions

DAFAK and HJM were involved in the conceptualization of the study. FDFAG was involved in data curation. FDFAG and DAFAK were involved in the formal analysis. DAFAK and HJM were involved in the investigative aspects of the study, in the study methodology and in project administration. HJM supervised the study. FDFAG and DAFAK were involved in the writing of the original draft of the manuscript. FDFAG, DAFAK and HJM were involved in the writing, reviewing and editing of the manuscript. All authors have read and approved the final manuscript. FDFAG and DAFAK both confirmed the authenticity of all the raw data.

Ethics approval and consent to participate

Written informed consent was obtained from all patients and the healthy individuals that were used as a control group. The study protocol was approved by the Ethics Committee of the Facility of Medicine of the University of Kufa, under the document reference MEC-02.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Khater MH, Abd El-Hassib DM, Sabry JH, Elkilany RM and Ameen SG: Association between renalase gene polymorphism (rs2296545) and hypertension in Egyptian chronic kidney disease patients. Cureus 15: e47903, 2023.
2. Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, Morgenstern H, Pavkov ME, Saran R, Powe NR, et al: Trends in prevalence of chronic kidney disease in the United States. Ann Intern Med 165: 473-481, 2016.
3. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY and Yang CW: Chronic kidney disease: Global dimension and perspectives. Lancet 382: 260-272, 2013.
4. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, Chen J and He J: A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. Kidney Int 88: 950-957, 2015.
5. Mallamaci F and Tripepi G: Risk factors of chronic kidney disease progression: Between old and new concepts. J Clin Med 13: 678, 2024.
6. Ahlawat RS, Gupta S, Kapoor S and Kar P: Polymorphism of renalase gene in patients of chronic kidney disease. Open J Nephrol 2: 136-143, 2012.
7. Naik RP, Derebail VK, Grams ME, Franceschini N, Auer PL, Peloso GM, Young BA, Lettre G, Peralta CA, Katz R, et al: Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. JAMA 312: 2115-2125, 2014.
8. O'Seaghdha CM, Parekh RS, Hwang SJ, Li M, Köttgen A, Coresh J, Yang Q, Fox CS and Kao WH: The MYH9/APOL1 region and chronic kidney disease in European-Americans. Hum Mol Genet 20: 2450-2456, 2011.
9. Ameer QZ: Hypertension in chronic kidney disease: What lies behind the scene. Front Pharmacol 13: 949260, 2022.
10. Erfanpoor S, Etemad K, Kazempour S, Hadaegh F, Hasani J, Azizi F, Parizadeh D and Khalili D: Diabetes, hypertension, and incidence of chronic kidney disease: Is there any multiplicative or additive interaction? Int J Endocrinol Metab 19: e101061, 2020.
11. Kushwaha R, Vardhan PS and Kushwaha PP: Chronic kidney disease interplay with comorbidities and carbohydrate metabolism: A review. Life (Basel) 14: 13, 2023.
12. Gerich JE: Physiology of glucose homeostasis. Diabetes Obes Metab 2: 345-350, 2000.
13. Kamal A: Estimation of blood urea (Bun) and serum creatinine level in patients of renal disorder. Indian J Fundam Appl Life Sci 4: 199-202, 2014.
14. Lousa I, Reis F, Beirão I, Alves R, Belo L and Santos-Silva A: New potential biomarkers for chronic kidney disease management-a review of the literature. Int J Mol Sci 22: 43, 2020.
15. Rehberg PB: Studies on kidney function: The rate of filtration and reabsorption in the human kidney. Biochem J 20: 447-460, 1926.

16. Bosch JP, Saccaggi A, Lauer A, Ronco C, Belledonne M and Glabman S: Renal functional reserve in humans. Effect of protein intake on glomerular filtration rate. Am J Med 75: 943-950, 1983.

17. Waikar SS and Bonventre JV: Creatinine kinetics and the definition of acute kidney injury. J Am Soc Nephrol 20: 672-679, 2009.

18. Stevens PE and Levin A: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Ann Intern Med 3: 825-831, 2013.

19. Gafter-Gvili A, Schechter A and Rozen-Zvi B: Iron deficiency anemia in chronic kidney disease. Acta Haematol 142: 44-50, 2019.

20. Gaweda AE: Markers of iron status in chronic kidney disease. Hemodial Int 21 (Suppl 1): S21-S27, 2017.

21. Poojar B, Ommurugan B, Adiga S, Thomas H, Sori RK, Poojar B, Hodlur N, Tilak A, Korde R and Gandigawad P: Methodology Used in the Study. Asian J Pharm Clin Res 7: 1-5, 2017.

22. Omari Shekaftik S and Nasirzadeh N: 8-Hydroxy-2'-deoxyguanosine (8-OHdG) as a biomarker of oxidative DNA damage induced by occupational exposure to nanomaterials: A systematic review. Nanotoxicology 15: 850-864, 2021.

23. Jacobson MH, Liu M, Wu Y, Furth S, Warady B, Trachtman H and Trasande L: Oxidant stress and renal function among children with chronic kidney disease: A repeated measures study. Sci Rep 10: 3129, 2020.

24. Okamura DM and Himmelfarb J: Tipping the redox balance of oxidative stress in fibrogenic pathways in chronic kidney disease. Pediatr Nephrol 24: 2309-2319, 2009.

25. Honda T, Hirakawa Y and Nangaku M: The role of oxidative stress and hypoxia in renal disease. Kidney Res Clin Pract 38: 414-426, 2019.

26. Goriuc A, Cojocaru KA, Luchian I, Ursu RG, Butnaru O and Foia L: Using 8-hydroxy-2'-deoxiguanosine (8-OHdG) as a reliable biomarker for assessing periodontal disease associated with diabetes. Int J Mol Sci 25: 1425, 2024.

27. Dhondup T and Qian Q: Acid-base and electrolyte disorders in patients with and without chronic kidney disease: An update. Kidney Dis (Basel) 3: 136-148, 2017.

28. Ray L, Nanda SK, Chatterjee A, Sarangi R and Ganguly S: A comparative study of serum aminotransferases in chronic kidney disease with and without end-stage renal disease: Need for new reference ranges. Int J Appl Basic Med Res 5: 31-35, 2015.

29. Cheng T, Wang X, Han Y, Hao J, Hu H and Hao L: The level of serum albumin is associated with renal prognosis and renal function decline in patients with chronic kidney disease. BMC Nephrol 24: 57, 2023.

30. Mehmood HR, Khan Z, Jahangir HMS, Hussain A, Elahi A and Askari SMH: Assessment of serum biochemical derangements and associated risk factors of chronic kidney disease. J Taibah Univ Med Sci 17: 376-383, 2021.

31. Kuhn C, Mohebbi N and Ritter A: Metabolic acidosis in chronic kidney disease: Mere consequence or also culprit? Pflugers Arch 476: 579-592, 2024.

32. Poznyak AV, Sadykhov NK, Kartuesov AG, Borisov EE, Sukhorukov VN and Orekhov AN: Atherosclerosis specific features in chronic kidney disease (CKD). Biomedicines 10: 2094, 2022.

33. Li J, Liu D and Liu Z: Serum Total bilirubin and progression of chronic kidney disease and mortality: A systematic review and meta-analysis. Front Med (Lausanne) 7: 549, 2021.

34. Taliercio JJ, Schold JD, Simon JF, Arrigain S, Tang A, Saab G, Nally JV Jr and Navaneethan SD: Prognostic importance of serum alkaline phosphatase in CKD stages 3-4 in a clinical population. Am J Kidney Dis 62: 703-710, 2013.

35. Gluba-Brzózka A, Franczyk B, Olszewski R and Rysz J: The influence of inflammation on anemia in CKD patients. Int J Mol Sci 21: 725, 2020.

36. McClellan WM, Flanders WD, Langston RD, Jurkovitz C and Presley R: Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: A population-based study. J Am Soc Nephrol 13: 1928-1936, 2002.

37. Guerra F, Di Giacomo D, Ranieri J, Tunno M, Piscitani L and Ferri C: Chronic kidney disease and its relationship with mental health: Allostatic load perspective for integrated care. J Pers Med 11: 1367, 2021.

38. Mizdrak M, Kumrić M, Kurir TT and Božić J: Emerging biomarkers for early detection of chronic kidney disease. J Pers Med 12: 548, 2022.

39. Vallianou NG, Mitesh S, Gkogkou A and Geladari E Chronic kidney disease and cardiovascular disease: Is there any relationship? Curr Cardiol Rev 15: 55-63, 2019.

40. Al-Wahsh H, Lam NN, Liu P, Quinn RR, Fiocco M, Hemmelgarn B, Tangri N, Tonelli M and Ravani P: Investigating the relationship between age and kidney failure in adults with category 4 chronic kidney disease. Can J Kidney Heal Dis 7: 2054358120966819, 2020.

41. Nguyen A, Khafagy R, Gao Y, Meerasa A, Roshandel D, Anvari M, Lin B, Cherney DZI, Farkouh ME, Shah BR, *et al*: Erratum. Association between obesity and chronic kidney disease: multivariable mendelian randomization analysis and observational data from a bariatric surgery cohort. Diabetes 2023;72:496-510. Diabetes 72: 1174, 2023.

42. Prasad R, Jha RK and Keerti A: Chronic kidney disease: Its relationship with obesity. Cureus 14: e30535, 2022.

43. Yang S, Ling J, Zhang S, Li Y and Yang G: Metabolic dysfunction, rather than obesity, is a risk factor for chronic kidney disease in Chinese population. Aging Male 27: 2335158, 2024.

44. Mather A and Pollock C: Glucose handling by the kidney. Kidney Int 79 (Suppl 120): S1-S6, 2011.

45. Wright EM, Hirayama BA and Loo DF: Active sugar transport in health and disease. J Intern Med 261: 32-43, 2007.

46. Merzah KS and Hasson SF: The biochemical changes in patients with chronic renal failure. Int J Pharma Med Biol Sci 4: 75-79, 2015.

47. Nisha R, Srinivasa Kannan SR, Thanga Mariappan K and Jagatha P: Biochemical evaluation of creatinine and urea in patients with renal failure undergoing hemodialysis. J Clin Pathol Lab Med 1: 1-5, 2017.

48. Pandya D, Nagrajappa AK and Ravi KS: Assessment and correlation of urea and creatinine levels in saliva and serum of patients with chronic kidney disease, diabetes and hypertension-A research study. J Clin Diagnostic Res 10: ZC58-ZC62, 2016.

49. Fujisawa H, Nakayama M, Haruyama N, Fukui A, Yoshitomi R, Tsuruya K, Nakano T and Kitazono T: Association between iron status markers and kidney outcome in patients with chronic kidney disease. Sci Rep 13: 18278, 2023.

50. Cavalcanti Sette LHB and de Almeida Lopes EP: Liver enzymes serum levels in patients with chronic kidney disease on hemodialysis: A comprehensive review. Clinics (Sao Paulo) 69: 271-278, 2014.

51. Sabouri S, Afzal Aghaee M, Lotfi Z, Esmaily H, Alizadeh M and Mozafari HM: Evaluation of liver enzymes in end-stage renal disease patients on the renal transplant-waiting list in north-west of Iran. Nephrourol Mon 12: e107859, 2020.

52. Crawford DR, Reyna RS and Weiner MW: Effects of in vivo and in vitro dialysis on plasma transaminase activity. Nephron 22: 418-422, 1978.

53. El-Khoury JM and Wang S: Aspartate aminotransferase and alanine aminotransferase. In: Kazmierczak SC and Azzazy HME (eds). Diagnostic Enzymology. Berlin, Germany: De Gruyter, pp81-104, 2014.

54. Cohen DL and Townsend RR: Central blood pressure and chronic kidney disease progression. Int J Nephrol 2011: 407801, 2011.

55. Beddhu S, Ma X, Baird B, Cheung AK and Greene T: Serum alkaline phosphatase and mortality in African Americans with chronic kidney disease. Clin J Am Soc Nephrol 4: 1805-1810, 2009.

56. O'Rourke MF and Safar ME: Relationship between aortic stiffening and microvascular disease in brain and kidney: Cause and logic of therapy. Hypertension 46: 200-204, 2005.

57. Gatua WK, Ngeranwa JJN and Mbugua P: The effects of chronic kidney disease on liver function tests: The laboratory interpretation perspective. Asian J Med Sci 10: 13-18, 2019.

58. Molla MD, Degef M, Bekele A, Geto Z, Challa F, Lejisa T, Getahun T, Sileshi M, Tolcha Y, Ashebir G and Seifu D: Assessment of serum electrolytes and kidney function test for screening of chronic kidney disease among ethiopian public health institute staff members, Addis Ababa, Ethiopia. BMC Nephrol 21: 494, 2020.

59. Lobo V, Patil A, Phatak A and Chandra N: Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev 4: 118-126, 2010.

60. Tarng DC, Wen Chen T, Huang TP, Chen CL, Liu TY and Wei YH: Increased oxidative damage to peripheral blood leukocyte DNA in chronic peritoneal dialysis patients. J Am Soc Nephrol 13: 1321-1330, 2002.

61. Sanchez M, Roussel R, Hadjadj S, Moutairou A, Marre M, Velho G and Mohammedi K: Plasma concentrations of 8-hydroxy-2'-deoxyguanosine and risk of kidney disease and death in individuals with type 1 diabetes. Diabetologia 61: 977-984, 2018.

62. Wojtaszek E, Oldakowska-Jedynak U, Kwiatkowska M, Glogowski T and Malyszko J: Uremic toxins, oxidative stress, atherosclerosis in chronic kidney disease, and kidney transplantation. Oxid Med Cell Longev 2021: 6651367, 2021.

63. Zoccali C, Mallamaci F, Adamczak M, de Oliveira RB, Massy ZA, Sarafidis P, Agarwal R, Mark PB, Kotanko P, Ferro CJ, *et al*: Cardiovascular complications in chronic kidney disease: A review from the European renal and cardiovascular medicine working group of the European renal association. Cardiovasc Res 119: 2017-2032, 2023.

64. Begum S and Latunde-Dada GO: Anemia of inflammation with an emphasis on chronic kidney disease. Nutrients 11: 2424, 2019.

65. Lewandowski MJ, Krenn S, Kurnikowski A, Bretschneider P, Sattler M, Schwaiger E, Antlanger M, Gauckler P, Pirklbauer M, Brunner M, *et al*: Chronic kidney disease is more prevalent among women but more men than women are under nephrological care: Analysis from six outpatient clinics in Austria 2019. Wien Klin Wochenschr 135: 89-96, 2023.