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Assessment of NGAL, KIM-1 and ADMA in chronic kidney disease patients in Wasit province, Iraq

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Abstract

The study highlights the importance of new biomarkers (NGAL, KIM-1 and ADMA) in predicting early onset and progression of chronic kidney disease. Using these markers alongside traditional measures like eGFR and serum creatinine provides a comprehensive understanding of chronic kidney disease severity, leading to improved diagnosis, treatment, and patient outcomes. This can enhance health policy, clinical practices, and medical education.

Introduction:

Kidney disease encompasses conditions that lead to functional or structural disorders of the kidney. It is characterized by a glomerular filtration rate (GFR) below 60 mL/min/m² for over three months or blood urea concentrations exceeding 80 µmol/L. More than 50% of cases result in lethality, with only a third of patients surviving longer than three months. Chronic kidney disease (CKD) and impaired renal function vary in severity but share common issues, such as proteinuria (≥100 mg albuminuria for over 90 days and a GFR< 60 mL/min/1.73 m^2). Early identification, timely treatment, and monitoring can prevent disease progression.

Methods: *The current clinical study aimed to evaluate the severity of CKD in 60 patients aged 18 to 85 years and compare them with 30 healthy controls, focusing on CKD stages 3 to 5.We utilized the estimated GFR (eGFR) to identify CKD, with stage 5 representing kidney failure occurring within three months. Serum creatinine was used as a crucial marker due to its free filtration and non-metabolization by renal tubules. New biomarkers, including, neutrophil gelatinase-associated lipocalin (NGAL), asymmetric dimethyl arginine (ADMA(, and kidney injury molecule-1 (KIM-1) were evaluated for their ability to predict early kidney disease onset and indicate inflammation. Data were collected through questionnaires from all participants, excluding those with cancer, viral hepatitis, or hormonal disorders.*

Results: *Our study established correlations between new biomarkers, disease severity, and eGFR. Statistically significant differences across disease stages were identified using the CKD-EPI formula, which considers creatinine level, age, gender, and race.*

Conclusion: *The study highlights the importance of new biomarkers in predicting early onset and progression of CKD. Monitoring these markers alongside traditional measures like eGFR and serum creatinine can provide*

a comprehensive understanding of disease severity and improve patient outcomes.

Keywords: *Chronic kidney disease, estimated GFR, proteinuria, serum creatinine, biomarkers, CKD-EPI formula, inflammation indicators.*

Introduction

Chronic non-transmittable condition of the kidneys is the chronic kidney disease which is characterized by impaired renal function and the slow decrease in glomerular filtration rate. More patients are in an asymptomatic stage until their renal function reduction gets to only 15-20% of their normal level, which makes us defined CKD as a silent disease. The glomerular filtration rate (GFR) (1), which evaluates how well the kidneys can filter blood, is a he most important and accurate measurement to show how well the kidneys work. Blood creatinine assays, used to examine glomerular filtration rate, are the first-choice diagnostic techniques for determination of kidney function (2). The glomerulus which is one of the parts of kidney which is used to filter serum creatinine is a breakdown product of creatine and creatine phosphate. The estimated GFR (eGFR) is standardized to 1.73 m^2(3).

The pathologies of the kidneys are characterized by five stages, ranging from mild renal dysfunction to complete failure, encompassing the full spectrum of chronic kidney disease (CKD) (4). Various diagnostic indicators for chronic kidney disease (CKD) have been assessed in recent years. While serum creatinine is commonly utilized to assess renal function, elevated levels of serum creatinine predominantly indicate glomerular filtration and should not be regarded as an optimal biomarker for assessing renal impairment, because it is not sensitive enough and is dependent on the mass of muscle, gender, and other factors(5). It's dependent on the age of the individual. Race, the medication may not be considered to be ideal biomarkers for causing kidney damage. The diagnosis of tubular injury is made when the rate of filtration is not reduced significantly (6). Moreover, due to its origin in the liver and its susceptibility to hepatic dysfunction, serum creatinine may not accurately reflect glomerular filtration rate (GFR) in specific disorders (7).

Biomarkers that can distinguish early harm and recognize patients at a higher gamble of creating moderate kidney infection would incredibly work on the determination and treatment of the condition. NGAL has been proposed as a practical solution for this disease. Subsequently, NGAL could be an extraordinary biomarker for the early discovery of constant kidney infection. This little glycoprotein is delivered into the granules of mature neutrophils, likewise named lipocalin-2, this protein is communicated in a populace of stressed cardiovascular myocytes and endothelial cells in the kidneys. (8). Utilizing both creatinine and cystatin C to work out glomerular filtration rate gives more noteworthy precision and prompts a more exact order of glomerular filtration rate estimated as under 60 mL/min/1.73 m as the limit for diagnosing CKD (9). Ensuing examinations in more seasoned populaces found that serum cystatin C is a more grounded indicator of all-cause mortality than creatinine (10).

In one review, KIM-1 showed some commitment as a potential biomarker in distinguishing ongoing kidney sicknesses of dubious etiology in cultivating networks in Sri Lanka. In a concentrate in a gathering of 4,739 patients, fasting plasma KIM-1 levels were fundamentally connected with a more prominent decrease in glomerular filtration rate (eGFR). The prescient worth of KIM-1 was additionally exhibited in an investigation of 894 patients with CKD. which showed that high plasma KIM-1 level were related with an expanded gamble of diabetic kidney sickness (11). For instance, a new investigation of Ongoing Renal Inadequacy Companion (CRIC) members with CKD showed that KIM-1 and NGAL levels were essentially connected with CKD movement. Be that as it may, when blood creatinine-subordinate glomerular filtration rate (eGFR) is controlled for, egg whites, which are customary markers of kidney capability, is not generally autonomously related with the advancement of CKD.

In addition, two potential biomarkers of tubular injury may have limited utility in patients with low renal reserve (12). According to a study conducted on adults, it was found that the concentration of dimethylarginine not only increases CKD but also increases its progression. They wanted to know if baseline serum dimethylarginine

affects BGR. Their results demonstrated that baseline serum dimethylarginine concentration inversely linked with glomerular basal filtration rate. ADMA levels correlate with creatinine clearance and eGFR, and greater levels are linked to hypertension and mortality (14) . The primary cause of mortality in chronic kidney disease (CKD), is cardiovascular disease (CVD), which is associated with dimethylarginine(15). In patients undergoing radiolysis, ADMA serves as a significant predictor(16).

Objectives

The objectives of this study was to estimate the prevalence of CKD in Wasit province and provide some aspects of new diagnostic tools through some biomarkers and investigate them in their possible association with the following:

1-Estimation of efficiency of GFR and its relation with hypertension and insulin resistance by neutrophil gelatinase-associated lipocalin (NGAL) and asymmetric dimethyl arginine (ADMA).

2-Estimate the risk of tubular injury and inflammation by the level of kidney injury molecule-1 (KIM-1) .

Patients and Methods

This clinical study included 60 patients. Iraqi patients with CKD in its three stages (III, IV and V) compared to 30 controls of both sexes, aged between 18 and 88 years, distributed between both sexes. Samples were collected from the dialysis center of Al-Zahraa Teaching Hospital in Wasit and some health centers in the governorate. During the period from 10/2022 to 4/2023. CKD patients were diagnosed by a specialist in kidney and urology surgery in stages 3, 4 and 5, based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. This equation is the preferred method for estimating the estimated glomerular filtration rate (eGFR). Our proposed general approach to calculating eGFR includes using the patient's serum creatinine level, age, gender and ethnicity, as these factors allow for accurate determination of the patient's diagnostic stage of kidney function.

Statistical analysis

The data were statistically analyzed using IBM Statistical Package for Social Sciences (SPSS 25) by finding the mean ± significant difference (mean ± standard error) using One- Way Analysis of Variance (ANOVA) analysis and taking ($P \geq 0.05$) as the minimum significance value to evaluate the differences between chronic renal failure patients in stage ((III, IV, V)) and the control group so that the cases of chronic kidney disease were compared with the control group of 60 patients and some physiological biomarkers were studied and there were statistically significant differences. Significant differences between data means determined by least significant differences (LSD).

Results

The study showed in Figure (1) that among 60 Patients aged from 18 to over 85 years, gathered from Al-Zahraa Teaching Hospital, the number of those suffering from advanced stages of chronic kidney disease gradually increased in stages from 3 to 5. It was compared with a control group consisting of a total of 30 people subdivided into (15) man and (15) woman between the ages of (18-40) years of age. StudiThe study in Figure (1) showed that among 60 patients aged 18 to over 85 years and of both sexes, the number of patients with advanced stages of CKD gradually increased from stage 3 to stage 5. They were compared with a control group of 30 people in total. Studies have repeatedly confirmed that renal gelatinase-associated lipocalin (NGAL) is a promising marker for the diagnosis of CKD. This statistical analysis aims to evaluate the diagnostic value of NGAL as well as KIM-1, BTP for CKD patients where patients were selected and diagnosed according to the stages of kidney function by finding the glomerular filtration rate based on the creatinine level, age and gender. The lower the glomerular filtration rate, the lower the kidney function and the disease reached an advanced state.es have repeatedly confirmed that renal gelatinase-associated lipocalin (NGAL) is a promising marker for the diagnosis of chronic kidney disease. This statistical analysis aims to evaluate the diagnostic value of NGAL for chronic kidney disease. As indicated in Table 1 below, the results of this study, consistent with previous research, confirm that there were highly statistically significant differences in the NGAL measurements for stages III, IV, and V. The comparison of patients with chronic renal disease to the control group showed respective NGAL values of (2.067±0.06) pg/mL, (4.940±0.59) pg/mL, (4.53±0.09) pg/mL, and (8.15±0.44) pg/mL.

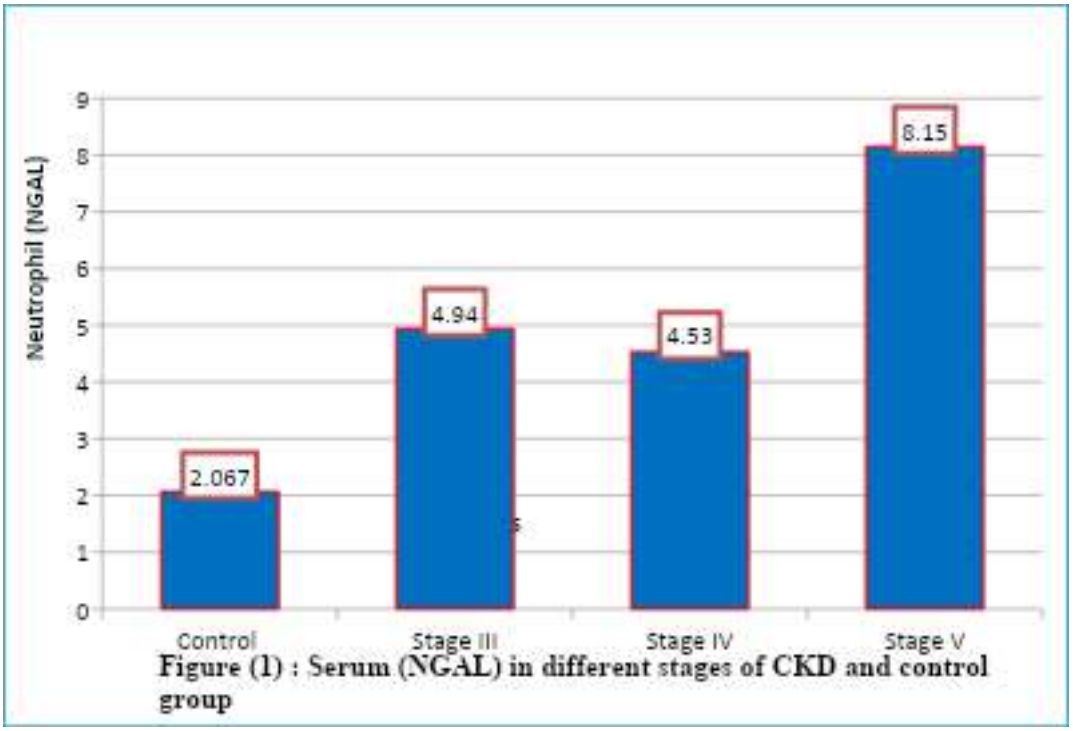

Figure (1) : Serum (NGAL) in different stages of CKD and control group

The values, as shown below in the Table (1) and Figure (2), are (516.80±20.93) ng/ml, (1514.83±36.49) ng/ml, (1636.87±68.46) ng/ml, and (2047.63±55.77) ng/ml.

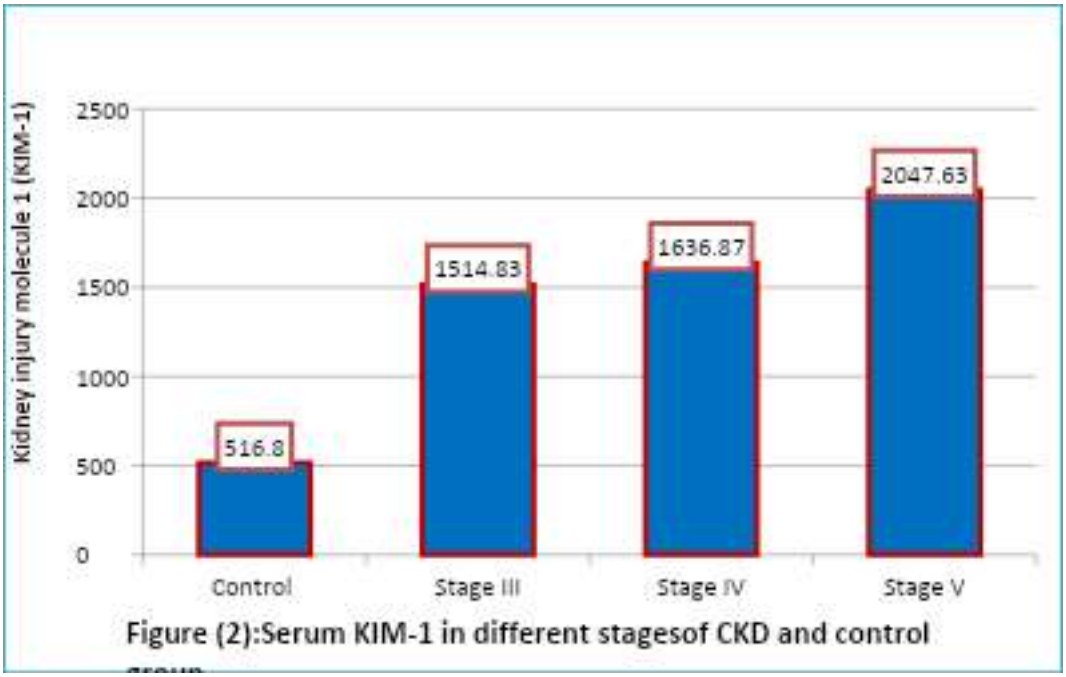

Figure (2):Serum KIM-1 in different stagesof CKD and control

Our study revealed that persons with eGFRs≤60 ml/min/1.73 m² have considerably greater average levels of asymmetric dimethylarginine (ADMA) compared to individuals with an eGFR≥60ml/min/1.73m². There was a significant inverse relationship observed between eGFR levels and ADMA concentrations in both

males and females. After accounting for factors such as gender, age, place of residence, education level, smoking status, and marital status, the negative relationship remained consistent among individuals with stage III, IV, and V chronic kidney disease (CKD), as well as among the control group. The eGFR values reported in Table (1) and Figure (3) were (23.27±1.13)µl, (99.61±7.76)µl, (113.47±3.91) µl, and (149.42±4.88) µl respectively.

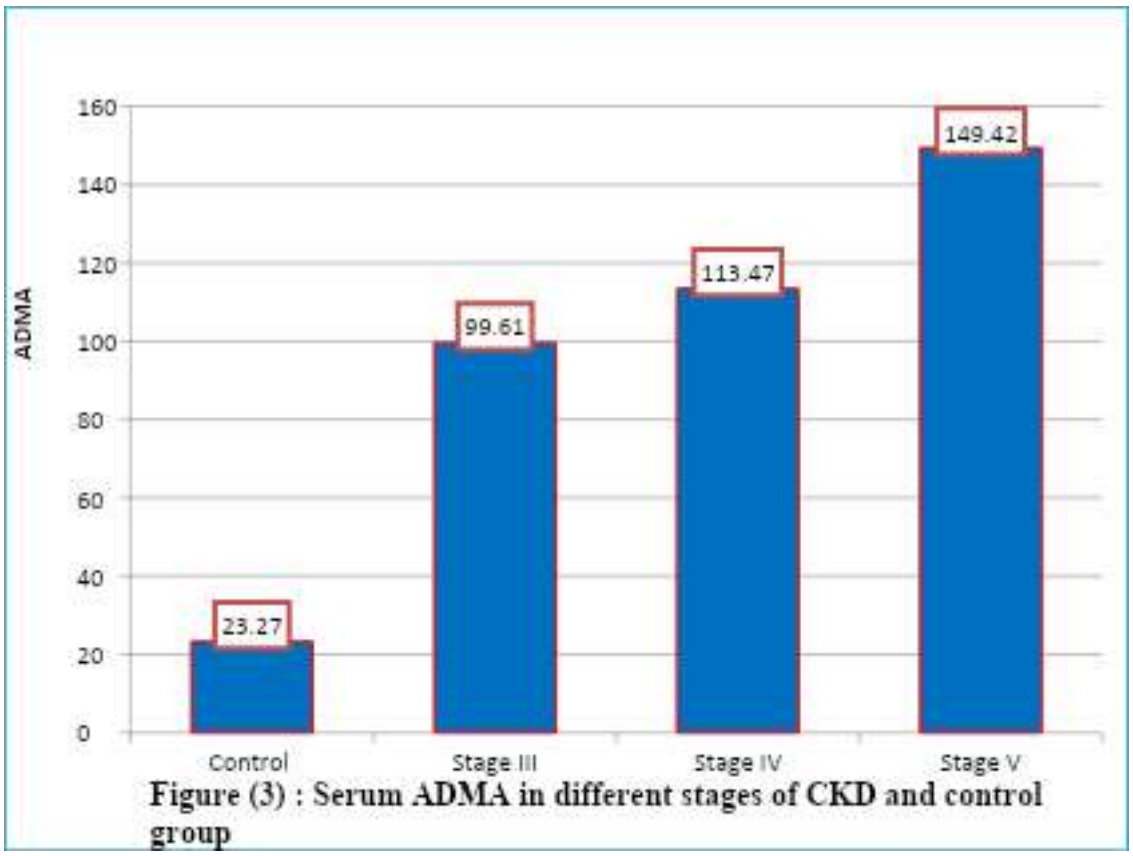

Figure (3) : Serum ADMA in different stages of CKD and control group

Table (1). Comparison between different stages of CKD and gelatinase-associated lipocalin (NGAL) pg/ml, kidney injury molecule-1 (KIM-1) ng/ml, and asymmetric dimethylarginine (ADMA) µl in serum with the control group.

Stages of CKD	Mean ± S.E		
	Neutrophil (NGAL) pg/ml	Kidney injury molecule 1 (KIM-1) ng/ml	Asymmetric dimethylarginine (ADMA) µl
Control	2.067 ±0.06 a	516.80 ±20.93 a	23.27 ±1.13 a
Stage III	4.940 ±0.59 b	1514.83±36.49 b	99.61 ±7.76 b
Stage IV	4.53 ±0.09 b	1636.87 ±68.46 b	113.47 ±3.91 c
Stage V	8.15 ±0.44 c	2047.63 ±55.77 c	149.42 ±4.88 d
L.S.D. value	0.957 **	127.36 **	12.81 **
P-value	0.0001	0.0001	0.0001

The presence of different letters for each mean means that there are significant differences between the means.

The presence of similar letters for each mean means that there are no significant differences between the means.

**refer to a significant differences at (P≤0.01).

L.S.D. refer to Least significant difference

S.E. refer to standard error

Discussion

Since the renal tubulointerstitial injury has been reported in a research context, the latter serves as a crucial mechanism for the development of chronic kidney disease (CKD) (17). Studies suggest that the gelatinase-associated lipocalin (NGAL) levels in patients' blood or urine increases in highly in a few hours following acute ischemia-reperfusion injury(18). For one, it also showed significant differences in the plasma levels of NGAL for some of the patients as compared to the control group, as had already been found in other studies. One of the CKD risk factors is age(19). Diabetes, hypertension, obesity and other related diseases also promote the development of this disease. Diabetic glomerulosclerosis and hypertensive nephrosclerosis have different pathological features indicator different pathological features and, potential, of cardiovascular disease. Hypertensive nephropathy is in the second place among causes of End Stage Renal Disease (ESRD) accounting for the number of ESRD patients that is lower than diabetes cases only(20). The first steps to detect the presence of this condition is either through proteinuria detection and/or kidney function decline (21).

Although elevated serum creatinine is primarily a marker of glomerular filtration, it has been suggested that NGAL may be an ideal biomarker for detecting early Chronic kidney disease renal function, specifically referring to the glomerular filtration capacity (22). The number is twenty-two. The findings of the present study revealed that, in certain instances, the levels of NGAL were elevated in comparison to the control group in the investigation conducted by (23). Moreover, (24) determined that elevated levels of circulating NGAL are linked to hypertension and insulin resistance because to NGAL's involvement in oxidative stress, endothelial dysfunction, inflammation, and hypertension. Use of NGAL to monitor patients with hypertension and predict chronic kidney disease. Based on the current findings, pNGAL is a more accurate indicator of early renal dysfunction in CKD than serum creatinine in the general hypertensive population.

The average percentage of gelatinase-associated lipocalin (NGAL), among other biochemical markers, was considerably greater in cases as compared to controls ($P < 0.05$) in Figure 1

To begin with, the present study confirms the results of former studies, showing a significantly higher expression of kidney injury molecule-1 (KIM-1) in the third, fourth, and fifth stages of the chronic renal disease in contrast to the healthy control group (1). The study quantified KIM-1 blood levels using the methodology outlined in reference (25). After being diagnosed, individuals exhibit increased levels that are related with a greater likelihood of evolving more severe acute tubular injury and tubulointerstitial inflammation. Kidney injury molecule-1 (KIM-1), also known as HAVCR1 or TIM-1, is a type I glycoprotein that was first identified as the receptor for hepatitis A virus (26). KIM-1 expression is significantly elevated in the proximal tubule. Animal models indicate that the initial rise in KIM-1 expression is advantageous, but prolonged overexpression of KIM-1 in the tubules can lead to gradual renal fibrosis (27). Recent research has shown that plasma KIM-1 is a contributing factor to the development of chronic renal disease (28).

The results are consistent with and suggest that the primary focus of the study is the advancement to renal failure, which is defined as the initiation of renal replacement therapy (dialysis or kidney transplantation) (29). Furthermore, there is evidence supporting the idea that tubular injury plays a role in the decline of kidney function, which is commonly observed in cases of acute renal failure (30). Our findings support and agree with (26).

KIM-1 has diagnostic importance for several renal illnesses and can evaluate non-invasively. Due to renal tubule injury. The expression of KIM-1 is markedly elevated in the proximal renal tubules due to hypoxia or nephrotoxic events. Nevertheless, there may be a correlation between tubular damage and the initiation of chronic renal disease. Elevated levels of KIM-1 in the bloodstream have repeatedly been associated with many forms of chronic kidney disease, including both common and uncommon glomerular, interstitial, and vascular disorders. KIM-1 serves as a highly responsive marker for tubular injury, and elevated levels of KIM-1 are linked to an increased probability of developing a disease. Renal failure. Research on uremic nephropathy has shown that KIM-1 is a risk factor for the development of nephropathy in the future, even when considering glomerular filtration rate (eGFR) and proteinuria (31).

Our results were similar in individuals with and without glomerular disease These conditions encompass glomerular disease and innate malformations of the kidney and urinary tract (32) . Within this investigation, we quantified the amounts of KIM-1 in the serum of individuals afflicted with chronic renal disease. We found that higher serum KIM-1 levels were associated with an increased risk of subsequent progression to renal failure and death compared with controls, which we demonstrate in the statistical evidence presented in Figure (2).

Our investigation confirms a significantly substantial difference between controls and chronic renal disease phases, supporting the findings (33), confirming the presence of reduced and increased asymmetrical glomerular filtration rate in the elderly. Methylarginine (ADMA) ratio. However, most studies examining the association between the two diseases have been conducted in patients with impaired Renal function specifically in the old population, as opposed to the general population. Thus, We examined the correlation between eGFR and ADMA levels in both urban and rural regions.

Studies have shown critical autonomous relationship among eGFR and ADMA focuses in more established adults across various age groups. They proposed that low eGFR potential risk factor for endothelial brokenness. Indeed, even in sound, more established adults without known kidney illness, diminished kidney capability might mean an expanded potential endothelial brokenness. Our results align with previous studies(34), showing that ADMA concentrations were significantly higher in patients with stages 4–5 chronic kidney disease (CKD) (eGFR $\leq$ 30 ml/min/1.73 m²) compared to those with stages 2-3 CKD (eGFR $\geq$ 30 ml/min/1.73 m²), according to a subsequent Austrian review. They additionally noticed expanded ADMA plasma fixations and diminished urinary ADMA discharge in patients with stage 4–5 ongoing kidney sickness. Accordingly, they proposed that diminished glomerular filtration rate might impact the high gathering of plasma ADMA fixations and decrease urinary ADMA discharge (35).

Earlier research involving 218 patients with both hypertension and diabetes demonstrated a negative correlation between asymmetric dimethylarginine (ADMA) concentrations and glomerular filtration rate (eGFR). The research, in addition, illustrated that eGFR levels have to drop by a certain extend to have association with chronic increase of ADMA(36). Furthermore, another cross-sectional study made among Ghanaian patients suffering from type 2 diabetes yielded remarkable results as there existed a pronounced link between ADMA levels and eGFR in patients with low eGFR. While it is possible that ADMA could be a potential biomarker of kidney damage, the levels of ADMA are related with the patients who have diabetes and eGFR (estimated glomerular filtration rate) decreased in this group of patients (34).

ADMA was first found in human urine in 1970 and then validated as a discovery by our group. Nitric oxide synthase (NOS) is the most powerful natural inhibitor and its concentration is high in patients struggling with end-stage renal disease (ESRD). The high levels of ADMA are considered as precursors for future cardiac events and death in the patients undergoing hemodialysis. People who fail to get along well with end-stage renal disease (ESRD) who require dialysis show the highest dose of ADMA. Alongside showing cardiovascular risk factors, ADMA works as a separate death risk indicator in chronic kidney disease (35).

Our current study revealed, through our findings, as shown in the bar graphs in Figure (15), the relationship between ADMA with the progressive stages of CKD, which is consistent with the study conducted by (37), who showed that ADMA levels gradually increased to significantly higher values compared to controls and patients in CKD stages 2, 3, 4, and 5. This close relationship with kidney function is confirmed by the presence of an inverse relationship between ADMA and eGFR, with relatively higher serum concentrations compared to controls and a progressive loss of kidney function..

Conclusion

Plasma gelatinase-associated lipocalin (NGAL) has been the subject of recent research as a potential biomarker for the early detection of renal failure.. Its comparison with serum creatinine has sparked interest in NGAL as a diagnostic tool. According to the current study, blood creatinine is not as good a marker of kidney dysfunction as NGAL has early chronic kidney disease.. Moreover, NGAL demonstrated superior sensitivity and specificity in diagnosing renal failure compared to creatinine. Patients with high blood pressure are more likely to lose kidney function and develop chronic renal disease since high blood pressure is a prevalent cause of the condition. It is important to consider NGAL's importance as a biomarker for telling the difference between different types of kidney disease in people with different cardiovascular diseases and for finding kidney failure early in other groups.

Our research revealed a positive correlation between elevated plasma KIM-1 levels and the likelihood and advancement of renal failure in patients with renal disease. The significant association with renal failure indicates that plasma KIM-1 could potentially function as a specific marker for kidney-related diseases, aiding in the prevention of their development. happen. Improving assessment of the risk of progression to renal failure in different populations. Kidney disease. We found an inverse connection between eGFR and ADMA concentrations in men and women aged 18–88. favorable connection with disease severity. Therefore, markers of endothelial dysfunction such as ADMA may be used as indicators of cardiovascular risk in CKD. ADMA is also associated with aging, hypertension, and the development of kidney failure and renal fibrosis.

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