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Original Article

Comparison of BTP, NGAL, KIM-1, & ADMA biomarkers in CKD and non-CKD subjects

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Abstract: Introduction: New biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), a member of the lipocalin family, and kidney injury molecule-1 (KIM-1) have been utilised in recent years to identify the development of chronic kidney disease (CKD). However, attempts to use them as broad markers to check for renal injury in patients and to pinpoint the kidney injury site have been unsuccessful. Therefore the search for an ideal panel of biomarkers predicting progression of CKD is still ongoing. The present study is designed to evaluate the biomarkers for CKD from NGAL, KIM-1, Beta trace protein (BTP) and Asymmetric dimethylarginine (ADMA). Materials and Methods: For this case-control study, 100 participants were selected on the basis of inclusion and exclusion criteria at the Index Medical College Hospital and Research Centre, Madhya Pradesh, there were 67 male subjects and 33 female CKD subjects and 100 non-CKD subjects (60 male and 40 female) matched for age and sex were taken from the hospital. Results: Between the CKD and non-CKD participants, the levels of BTP, plasma NGAL, KIM-1, and ADMA were compared and found to be substantially higher than those in the controls. Conclusion: Abnormal renal function is linked to disturbed blood levels of BTP, NGAL, KIM-1, and ADMA. Strong correlations exist between increased blood levels of BTP, NGAL, KIM-1, and ADMA and reduced kidney function. They might thus be used to estimate the decline of renal function and the progression of CKD.

Keywords: CKD, BTP, NGAL, KIM-1, ADMA

Introduction

Chronic kidney disease (CKD) has become one of the most common non-communicable disorders causing mortality worldwide. More than 10% of whole world general population was affected from this condition which was nearly 800 million individuals, and the CKD burden in Asia was 11.2%. Of these, 8.6% was in East Asia, 12.0% in Southeast Asia, 13.1% in Western Asia, and 13.5% in South Asia. Three main countries that were contributing the maximum burden of CKD in Asia had high CKD prevalence rates were Thailand (12.4%), India (11.7%) and Malaysia (9.0%) respectively and become large burden on low- and middle-income countries as shown increasing in its associated deaths over the past 2 decades. Once renal damage is initiated, factors such as proteinuria, inadequate glycemic and blood pressure control, and developmental factors contribute to the progression of the disease to end-stage [1, 2].

Abnormalities in kidney function tests, such as GFR, and renal disease indicators, such stage as albuminuria or proteinuria, for a minimum of three months confirmed the presence of CKD. There are 5 stages of chronic kidney disease, starting with mild kidney impairment and progressing to complete kidney failure. The prognosis and course of therapy for CKD were variables. Treatment aims to slow the progression of the disease, reduce symptoms, and prevent complications. Treatments for CKD range from lifestyle changes like diet and exercise to medical interventions including blood pressure and glucose monitoring and drugs to lower proteinuria and complications. The efficacy of treatment was conditional on the nature and degree of the patient's ailment as well as their willingness to take medication as prescribed. Early diagnosis and treatment of CKD has the potential to halt the progression of the illness and improve patient outcomes. Many people with

end-stage renal disease need dialysis or a kidney transplant since there was no treatment for their condition. Therefore, CKD outcomes and quality of life were enhanced by early diagnosis and treatment [3, 4].

According to the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline, a GFR of 90 mL/min/1.73 represents healthy kidneys and the value less than 15 mL/min/1.73 indicates the end stage of kidney disease. A GFR of less than 60 mL/min/1.73 for more than three months is the common threshold for diagnosing CKD. Inulin clearance was a commonly used gold standard technique to assess glomerular filtration rate (GFR). A different approach was employed to determine GFR value despite the intrusive, time-consuming, and expensive nature of inulin clearance measurement. Consequently, the simplest and most often used measures for evaluating kidney function are serum creatinine levels and estimated glomerular filtration rate (eGFR) [5].

New biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), a member of the lipocalin family, and kidney injury molecule-1 (KIM-1), a type 1 transmembrane glycoprotein, have been utilised in recent years to identify the development of CKD [6-12].

Human Neutrophil gelatinase-associated lipocalin (NGAL) was 25 kDa secretory glycoprotein belonging to lipocalin superfamily. It was expressed in kidneys and other organs in response to tissue injury. NGAL was present in serum and urine at very low levels in healthy subjects. The 25 kDa secretory glycoprotein known as Human Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a member of the lipocalin superfamily. After tissue damage, it was expressed in the kidneys and other organs. In healthy participants, extremely little amounts of NGAL were found in the serum and urine. NGAL is a protease-resistant polypeptide that is easily excreted. It is released from the distal tubules, secreted with the urine or backleaking to the plasma, freely filtered, and then reabsorbed in the proximal tubules through endocytic megalin receptors. The majority of studies indicates that NGAL has a protective function in the course of CKD; also, NGAL has recently been acknowledged as another useful marker for the early identification of CKD [6-9, 13, 14].

Asymmetric dimethylarginine (ADMA) is an amino acid that occurs naturally [15]. ADMA can regulates NO in the kidney, controlling a number of significant processes [16]. The metabolism of ADMA depends heavily on the kidneys, which also excrete ADMA and express significant quantities of DDAH. Because ADMA is among the uremic poisons. A decrease in renal excretion, a reduction in enzymatic metabolism, and an increase in ADMA synthesis are the likeliest three causes of an increase in plasma ADMA. While it has been demonstrated that the first two processes play a role in raising ADMA levels in kidney illness. Although the kidneys do eliminate some ADMA, the main cause of its rise in kidney illness is impaired ADMA metabolism. Plasma ADMA levels in CKD patients may be able to predict the development of renal damage, cardiovascular risk, and mortality [10-12].

Kidney Injury Molecule-1 (KIM-1) as a type I membrane protein of 104 kDa that is expressed in the liver and kidney [17]. Phosphatidylserine receptor KIM-1 giving kidney epithelial cells a phagocytic phenotype. These phosphatidylserine epitopes and KIM-1 work together to phagocytose necrotic and apoptotic material from the tubule lumen. phagocytic elimination of apoptotic cells was markedly reduced by either accelerated shedding or an abundance of soluble KIM-1 in the extracellular matrix [18].

BTP is a low molecular weight protein that is virtually entirely eliminated by the kidneys and is readily filtered by the glomerulus without secretion or reabsorption in renal tubules. Increased BTP concentrations in serum indicate decreased protein clearance. Changes in body composition have no effect on this measurement. Thyroid function and the use of corticosteroids have no impact on its serum levels. Because of its reduced molecular mass, anionic characteristic, steady production rate, and stability, it is used to identify renal illness [19-25].

Serum creatinine, serum urea nitrogen, and creatinine clearance are the most often utilised serologic indicators for the diagnosis of renal disease, however they are all non-specific and insensitive for the identification of renal injury. NGAL, KIM-1, ADMA, and BTP are some of the newer biomarkers used to detect the onset of

CKD. The purpose of this study is to assess the NGAL, KIM-1, BTP, and ADMA biomarkers for CKD as part of the ongoing search for an optimum panel of biomarkers predicting in CKD. This study's originality consists in the finding of a previously unrecognized panel of biomarkers that may aid in the early detection of CKD and in its prevention and treatment.

Materials and methods

Location

In this study, participants will be selected on the basis of inclusion and exclusion criteria, attending the outpatient department (OPD) and in patient Department (IPD) of Department of Medicine at Index Medical College Hospital & Research Centre, Indore, Madhya Pradesh. The collected samples will be analysed for serum NGAL, ADMA, KIM-1, BTP, Urea and Creatinine at hospital laboratory.

Study design

For this case control study, all enrolled participants will be subjected to demographic, anthropometric and biochemical analysis following the standard protocols mentioned below in their respective segments. The detailed history with full clinical examination will be taken in all the cases. After providing all the necessaries details about this study an informed written consent will be obtained from the study participants prior to their enrolment in this study. Only consenting participants will be included in the study. Confidentiality of collected data will be upheld throughout this study.

Ethical clearance: The research study received ethical clearance from the Ethics and Research Committee of Index Medical College Hospital & Research Centre in Indore, Madhya Pradesh (Approval No: MU/MM/BNS/2021/46, dated 11/11/2021).

Study period: This study was conducted from December 2021 to January 2023.

Selection criteria

Inclusion criteria: (1) Patients with established diagnosis of CKD. (2) Age >18 years.

Exclusion criteria: (1) Primary tubular diseases. (2) Recent or concurrent administration of potentially nephrotoxic drugs. (3) Acute kidney injury. (4) Terminal kidney failure requiring dialysis. (5) Patients with known neurological disease.

Diagnostic criteria of CKD: CKD was diagnosed by measuring blood creatinine levels and estimating GFR. A GFR of 60 mL/min or less was used as a threshold for confirming CKD.

Sample size

100 patients of known CKD and 100 healthy individuals.

Sample collection

The detailed history with full clinical examination will be taken in all the cases. After providing all the necessaries details about this study an informed written consent will be obtained from the study participants prior to their enrolment in this study. Only consenting participants: will be included in the study.

Statistical analysis

The statistical analysis was conducted using the IBM SPSS Statistics software version 20.0 for Windows. Continuous variables were presented as mean ± standard deviation (SD). An independent t-test was employed to compare the parameters between the case and control groups, with a *p*-value of less than 0.05 considered statistically significant. The correlation between the parameters was assessed using the Karl Pearson's coefficient test.

Results

A total of 100 subjects with CKD were enrolled based on the inclusion and exclusion criteria. Among them, 67% were male and 33% were female. Additionally, 100 non-CKD subjects (60% male and 40% female) matched for age and sex were selected from the hospital, as shown in **Table 1**.

Comparison between CKD and non-CKD participants

Between CKD and non-CKD participants, the levels of urea, creatinine, creatinine clearance, BTP, plasma NGAL, KIM-1, and ADMA were compared using an independent t-test. Urea levels, which were 97.74±41.60 mg/dL on aver-

Table 1. Distribution of CKD subjects and non-CKD subjects by gender

	CKD	non-CKD	Total
Female	33%	40%	73 (36.5%)
Male	67%	60%	127 (63.5%)
Total	100%	100%	200 (100%)

Table 2. Comparison of urea, creatinine, creatinine clearance rate, BTP, plasma NGAL, KIM-1 and ADMA levels between the CKD and non-CKD subjects by independent t-test

	Case	Control	t value	*p* value
	Mean ± S.D.	Mean ± S.D.		
UREA (mg/dl)	97.74±41.60	27.47±5.06	16.77	<0.001**
CREAT (mg/dl)	2.12±0.48	0.78±0.10	27.48	<0.001**
Ccr	36.00±10.18	96.56±9.50	-43.48	<0.001**
BTP (ng/ml)	60.82±12.34	31.69±8.97	19.10	<0.001**
Plasma NGAL	298.10±65.35	108.28±46.92	23.60	<0.001**
KIM-1	140.68±50.97	108.86±35.43	5.13	<0.001**
ADMA	77.77±16.52	45.75±13.90	1483	<0.001**

**Correlation is significant at the 0.05 level.

age, were substantially higher in CKD patients than in controls (27.47±5.06 mg/dL) with a *p* value of less than 0.05. When compared to controls, who had mean creatinine levels of 0.78±0.10 mg/dL, participants with CKD had mean levels of 2.12±0.48 mg/dL, a significant increase with a *p* value less than 0.05. In CKD participants, the mean SD levels of creatinine clearance were 36.00±10.18 mg/dL, which was substantially lower than the 96.56±9.50 mg/dL in controls with a *p* value less than 0.05. In CKD participants, the mean ± SD levels of BTP were 60.82±12.34 mg/dL, which were substantially higher than the mean levels in controls, 31.69±8.97 mg/dL, with a *p* value less than 0.05. The mean NGAL levels were 298.10±65.35 mg/dL on average, which was considerably higher in CKD patients than in controls (108.28±46.92 mg/dL on average), according to a *p* value of less than 0.05. KIM-1 levels were 140.68±50.97 mg/dL on average (standard deviation), which was substantially higher in CKD patients compared to controls (108.86±35.43 mg/dL) with a *p* value less than 0.05. When compared to controls, who had mean ADMA levels of 45.75±13.90 mg/dL, CKD participants had mean ADMA levels of 77.77±16.52 mg/dL, which were substantially higher with a *p* value less than 0.05. As shown in **Table 2**.

Association between creatinine clearance with BTP, NGAL, KIM-1 and ADMA

Significant negative correlations were observed between creatinine clearance and BTP, NGAL, KIM-1, and ADMA, with r values of -0.655, -0.281, -0.650, and -0.581, respectively, as shown in **Table 3**. It means that the creatinine clearance is dependent on BTP, NGAL, KIM-1 and ADMA.

Association between urea with BTP, NGAL, KIM-1 and ADMA

Significant positive correlations were observed between urea and BTP, NGAL, KIM-1, and ADMA, with r values of 0.941, 0.550, 0.667, and 0.656, respectively, as shown in **Table 4**. It means that the urea is dependent on BTP, NGAL, KIM-1 and ADMA.

Association between serum creatinine with BTP, NGAL, KIM-1 and ADMA

Significant positive correlations were observed between serum creatinine and BTP, NGAL, KIM-1, and ADMA, with r values of 0.926, 0.689, 0.584, and 0.716, respectively, as shown in **Table 5**. It means that the Creatinine is dependent on BTP, NGAL, KIM-1 and ADMA.

Discussion

As CKD progresses, the body begins to retain metabolic wastes, salt, and water, which causes edema, heart failure, arrhythmia, changes in pigmentation, insulin resistance, hyperparathyroidism, elevations in pituitary and pancreatic hormone levels, thiamine and calciferol insufficiencies, liver infection, amenorrhea, dyslipidemia, and hyperhomocysteinemia severely affecting other organs [26, 27]. By making an early diagnosis and giving the condition the right care, doctors might slow down its progression and lessen its effects. Researchers have developed a range of indicators in previous years for assessing kidney function. Given its decline following structural kidney injury, the

Table 3. Correlation between creatinine clearance with BTP, NGAL, KIM-1 and ADMA in CKD subjects by Karl Pearson's correlation coefficient method

	r value	*p* value
BTP	-0.655	<0.001**
NGAL	-0.281	0.005**
KIM-1	-0.650	<0.001**
ADMA	-0.581	<0.001**

**Correlation is significant at the 0.05 level.

Table 4. Correlation between urea with BTP, NGAL, KIM-1 and ADMA in CKD subjects by Karl Pearson's correlation coefficient method

	r value	*p* value
BTP	0.941	<0.001**
NGAL	0.550	<0.001**
KIM-1	0.667	<0.001**
ADMA	0.656	<0.001**

**Correlation is significant at the 0.05 level.

glomerular filtration rate (GFR) was known as the best indicator of renal function among those measures. Numerous other renal functions in CKD patients also declined along with GFR [28, 29]. According to the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practise guideline, healthy kidneys have a GFR of 90 mL/min/1.73, whereas kidney disease that has reached its latter stages is indicated by a value of less than 15 mL/min/1.73. For more than three months, a GFR value of less than 60 mL/min/1.73 is considered as the typical cutoff for CKD. As direct testing of GFR was challenging, alternative approaches were used to assess the filtration efficiency of exogenous chemicals [5].

In this case-control research, the blood BTP levels of 100 CKD patients and 100 non-CKD participants were examined. Using these, we discovered that CKD participants had significantly higher serum BTP levels than non-CKD subjects (P=0.001). Additionally, this study revealed a strong positive correlation between BTP, urea, and creatinine levels (P<0.05). A significantly negative correlation between BTP levels and creatinine clearance was also observed. Several studies have found that individuals with chronic kidney disease exhibit a gradual increase in blood levels of beta-trace protein. These findings led the researchers to hypothesize that BTP is a simple assay that could serve as a reliable blood marker for assessing the degree of renal failure in individuals with CKD, potentially replacing the use of endogenous GFR [20-25].

Table 5. Correlation between creatinine with BTP, NGAL, KIM-1 and ADMA in CKD subjects by Karl Pearson's correlation coefficient method

	r value	*p* value
BTP	0.926	<0.001**
NGAL	0.689	<0.001**
BTP-1	0.584	<0.001**
ADMA	0.716	<0.001**

**Correlation is significant at the 0.05 level.

The present study found that serum NGAL levels were significantly higher in CKD subjects compared to non-CKD subjects (P<0.001). This study also demonstrated a significant positive correlation between NGAL, urea, and creatinine (P<0.05). NGAL levels also exhibited a significant negative correlation with creatinine clearance. Similar results have been reported in multiple studies, indicating that NGAL is a highly sensitive biomarker with lower specificity for CKD. So that NGAL could be utilized as a single reliable biomarker for early detection of CKD [6-9, 14]. On the other hand, some studies reported contradicting results compared to our study and they did not observed any significant associations of NGAL with CKD [30, 31].

Proximal tubular damage has been associated with KIM-1. While its importance in the serum is still unknown, it has been identified as a biomarker for acute renal damage and chronic kidney disease. Therefore, we conducted this study to identify serum KIM-1 levels and their relation to altered kidney function. We found that serum KIM-1 levels were significantly higher in CKD subjects compared with non-CKD subjects (P≤0.001). Similarly, this study also demonstrated a significant positive correlation between KIM-1, urea, and creatinine levels (P<0.05). KIM-1 levels also exhibited a significant negative correlation with creatinine clearance. Similar results were reported from many studies that KIM-1 levels were correlated with renal parameters in patients and found that serum KIM-1 levels appeared to be highly correlated with renal characteristics [32-35].

ADMA is involved in the etiology of various human disorders, including SLE, CKD, and ESRD. Therefore, we investigated serum ADMA levels to assess its role in CKD. In our study, we found that serum ADMA levels were higher in CKD subjects compared to non-CKD subjects. Our study results also showed a significant positive correlation between serum ADMA levels, urea, and creatinine ($P<0.05$) and negative correlated with creatinine clearance. Few studies were supported our results that serum ADMA levels were linked to chronic kidney failure, and serum ADMA levels elevated as kidney function decreased [10-12]. On the other hand, a few studies reported conflicting results and found no association between serum ADMA levels and CKD [34, 35].

Overall, the study results suggest that serum levels of BTP, NGAL, KIM-1, and ADMA have the potential to be helpful in the diagnosis and monitoring of CKD, as indicated by the results of this study. Based on these findings, BTP may be a valuable biomarker for determining the severity of CKD, as BTP levels are much higher in patients with CKD compared to healthy controls and there is a positive relation between BTP and urea and creatinine levels. Similarly, there was a positive association between NGAL and both urea and creatinine levels, suggesting that NGAL, similar urea, may be a valuable biomarker for the early diagnosis of CKD. NGAL levels were also shown to be considerably higher in CKD patients compared to healthy controls. This study's findings also suggest that KIM-1 may be a useful biomarker for assessing kidney function in CKD patients, as its levels are significantly higher in patients with CKD compared to healthy controls and there is a significant inverse relation between KIM-1 levels and creatinine clearance. Similarly, the results of this study show that ADMA levels are significantly higher in patients with CKD compared to healthy controls, and there is a negative correlation between serum ADMA levels and creatinine clearance, indicating that ADMA may also be a useful biomarker for assessing kidney function in CKD patients.

Conclusion

Serum levels of BTP, NGAL, KIM-1, and ADMA were found to be considerably greater in patients with CKD compared to those without CKD in this case-control investigation. A strong inverse association were found between BTP NGAL, KIM-1, and ADMA with creatinine clearance, and positive correlations between BTP, NGAL, KIM-1, and ADMA with urea and creatinine levels were also observed. These findings suggest the potential role of BTP, NGAL, KIM-1, and ADMA as blood biomarkers in evaluating CKD severity and progression. Therefore, regular monitoring of these biomarkers could aid in the early detection and diagnosis of CKD, facilitating prompt intervention and management to prevent further kidney damage and improve patients' outcomes.

Limitations and future scope of the study

Several study limitations exist. It is a case-control study, thus it cannot prove that CKD causes the biomarkers (BTP, NGAL, KIM-1, and ADMA). The study's small sample size and single-center design may limit its generalizability. The study did not assess biomarker levels longitudinally, which could have revealed the predictive power of these biomarkers for CKD onset and progression. Future research should validate this study's findings and determine the biomarkers' clinical utility in CKD diagnosis and management in larger longitudinal studies in diverse populations. Combining biomarkers may improve diagnostic accuracy and prediction in future studies. Finally, further studies are needed to understand the mechanisms by which these indicators contribute to CKD and to identify potential treatment targets.

Disclosure of conflict of interest

None.

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