Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [7] June 2024: 80-87

Online ISSN 2277-1808
Journal's URL: http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Exploring Traditional and Novel Diagnostic Biomarkers for Renal Disease: A Comprehensive Review

Kunal Ravindra Bahalkar[1], Aakansha Sanjaykumar Mishra [1]
Department of Pharmacology, Parul Institute of Pharmacy and Research, Parul University, Vadodara-391760, Gujarat, India.
Corresponding Author: Jagdish Kakadiya*
Email: jagdishkakadiya@gmail.com

ABSTRACT
Screening for kidney damage is of vital importance due to its current prevalence worldwide. Kidney damage biomarkers are essential for the diagnosis and follow-up of kidney damage. These include novel biomarkers like kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C, as well as traditional biomarkers like serum creatinine and proteinuria. This thorough review covers all aspects of renal damage, which includes its causes, types (prerenal, intrinsic, and postrenal), epidemiology, pathophysiology, signs and symptoms, investigations, and biomarkers. Renal injury arises from various factors such as infections, medications, autoimmune conditions, and hypertension, necessitating timely identification and management to prevent further deterioration and mitigate risks of chronic kidney disease (CKD) or kidney failure. Acute kidney injury (AKI) and CKD are significant public health concerns, with AKI posing notable risks, particularly in hospitalised patients. The pathophysiology of renal injury differs between AKI and CKD, with AKI characterised by abrupt decline and CKD by gradual deterioration of renal function. Symptoms include changes in urine output, oedema, fatigue, cognitive difficulties, and nausea. Diagnostic modalities encompass blood and urine analyses, imaging studies, and renal biopsies, with biomarkers like creatinine, cystatin C, and NGAL instrumental in assessing renal function. Renal damage classification into prerenal, intrinsic, and postrenal causes aids in targeted management. Electrolyte imbalances and proteinuria serve as important indicators of renal function. Overall, this review underscores the complex nature of renal damage and the necessity of a multidisciplinary approach to its diagnosis and management to improve patient outcomes.
Keywords: *Kidney injury, biomarkers, creatinine, uric acid, blood urea nitrogen.*

Received 09.04.2024 Revised 29.04.2024 Accepted 03.06.2024

INTRODUCTION

Renal damage denotes structural or functional impairment affecting the kidneys, influenced by various factors such as infections, medications, autoimmune conditions, and hypertension. Timely identification and effective management are imperative to forestall further deterioration in renal function and mitigate the risks of CKD or kidney failure [1]. Renal injury is categorized into prerenal, intrinsic, and postrenal causes, each characterized by distinct pathophysiological mechanisms. CKD and AKI pose significant public health challenges, particularly impacting low- and middle-income regions. AKI presents a notable risk of severe complications, particularly in hospitalized individuals. The pathophysiology of renal injury varies with AKI typically stemming from abrupt renal function decline, whereas CKD progresses gradually over time. Symptoms of renal injury encompass urine output changes, oedema, fatigue, cognitive difficulties, nausea, vomiting, and dyspnea. Diagnostic modalities include blood and urine analyses, imaging studies, renal biopsies, and urine output monitoring [2]. Biomarkers such as creatinine, blood urea nitrogen, cystatin C, NGAL, KIM-1, Interlucin-1 (IL-18), netrin-1, B2-microglobulin, monocyte chemotactic peptide-1 (MCP-1), electrolytes, proteinuria, and uric acid are instrumental in assessing renal function and discerning injury etiology. Treatment entails a multifaceted approach involving pharmacotherapy, lifestyle modifications, and occasionally surgical interventions, emphasizing the critical role of early detection and intervention in optimizing long-term outcomes [3].

Types: AKI can be classified into three main types: prerenal, intrarenal, and postrenal, each with distinct causes and mechanisms. Prerenal AKI is characterized by decreased blood flow to the kidneys, leading to reduced perfusion. This type can be caused by various factors such as severe dehydration, heart failure, shock, and conditions affecting the blood vessels that supply the kidneys. Common triggers include

hypovolemic states (like haemorrhage or severe burns), systolic heart failure, hypoalbuminemia, and certain medications such as NSAIDs, ACE inhibitors, or iodinated contrast agents. Intrinsic or intrarenal AKI occurs due to damage to the kidney tissue itself, affecting the functional parenchyma. Causes of this type include acute tubular necrosis (often triggered by ischemia or exposure to nephrotoxic substances like aminoglycosides or methotrexate), glomerulonephritis, interstitial nephritis, and renal artery thrombosis [4]. Postrenal AKI results from urinary tract obstruction, hindering urine flow from the kidneys. Causes of this obstruction can vary from kidney stones and tumours to conditions like benign prostatic hyperplasia, prostate cancer, or intra-abdominal tumours [5].

Etiology: The etiology of AKI and CKD presents a spectrum of factors. AKI may arise from prerenal, intrinsic, or postrenal causes. Prerenal AKI results from insufficient renal perfusion, whereas intrinsic AKI encompasses various kidney diseases or damage, including nephrotoxins, glomerulonephritis, interstitial nephritis, and acute tubular necrosis (ATN) [6]. Postrenal AKI stems from obstructive conditions in the urinary tract distal to the kidneys. Additionally, AKI can manifest due to diseases like rhabdomyolysis, tumour lysis syndrome, multiple myeloma, and microangiopathies. CKD exhibits diverse aetiologies, with diabetes and hypertension serving as predominant causes [7]. Other contributors include glomerulonephritis, interstitial nephritis, and polycystic kidney disease. CKD can also result from AKI, potentially leading to its development or exacerbation. The pathogenesis of CKD is multifaceted, involving mechanisms such as inflammation, oxidative stress, and fibrosis [8].

Epidemiology: The epidemiology of kidney damage, encompassing AKI and CKD, reveals a substantial global burden with a multifaceted etiology. The reported incidence of AKI exhibits notable variability across studies and settings, spanning from 5.7% to 65.8% [9]. Factors contributing to AKI incidence divergence include regional disparities, with conditions such as sepsis, tropical illnesses, toxins, envenomation, and obstetrical complications assuming greater prominence in specific geographical areas [10]. In the United States, CKD affects over 1 in 7 adults, yet approximately 90% of affected individuals remain unaware of their condition. Demographic factors such as sex, race, and ethnicity influence CKD prevalence, with non-Hispanic Black adults exhibiting a higher prevalence compared to other racial and ethnic groups [11]. The epidemiological landscape of kidney damage underscores the imperative for preventive measures, early detection strategies, and comprehensive management approaches to alleviate their public health impact [12].

Pathophysiology: The pathophysiology of kidney injury encompasses various mechanisms contingent upon the specific type of injury, notably AKI and CKD. AKI typically arises from a sudden decline in renal function, often attributed to factors such as diminished blood flow, intrinsic renal pathologies, or obstructive processes. Ischemia-related insults pose a significant risk to renal integrity, eliciting vasoconstriction, endothelial damage, and inflammatory cascades. Additionally, renal toxicity may ensue from hemodynamic shifts, direct cellular and tissue injury, or impediments to renal excretion. Conversely, CKD manifests as a progressive deterioration of renal function, commonly associated with conditions like diabetes and hypertension [13]. The pathophysiology of CKD entails a gradual decline in kidney function over time, characterized by the accumulation of waste products and fluids within the body. This deterioration results from diverse factors including inflammation, fibrosis, and programmed cell death. Underlying glomerular or tubular injuries often prompt the release of vasoconstrictive agents due to prolonged ischemic insults, septic episodes, or nephrotoxic substances. In both AKI and CKD, intricate interactions among various cellular and molecular pathways contribute to impaired kidney function. If left untreated, these conditions can precipitate severe complications and adverse health outcomes. Renal injury can be further categorized into prerenal, intrarenal, and postrenal forms, with hypoperfusion leading to prerenal azotemia and potential progression to renal injury. Distinguishing between prerenal and intrarenal forms can be challenging, particularly in cases of primary intrarenal injury such as acute glomerulonephritis. Postrenal kidney injury typically arises from urinary tract obstruction at various levels [14]. ATN represents a major pathological correlate of intrarenal AKI, accounting for a significant portion of AKI cases. The pathophysiology of AKI involves a complex interplay of vascular, tubular, and inflammatory factors, with subsequent repair processes either restoring epithelial function or culminating in fibrotic remodelling, potentially leading to CKD. Innate and acquired immunity play crucial roles in injury regulation and repair processes. The susceptibility of S3-segment epithelial cells of the proximal tubules to ischemic and toxic insults underscores their pivotal role in epithelial reconstitution during the repair phase [15].

Signs and symptoms: Symptoms of kidney injury, particularly AKI, encompass a range of physiological disruptions. These include reduced urinary output, often accompanied by peripheral oedema in the lower limbs, ankles, and periorbital areas. Fatigue or asthenia may ensue, compounded by dyspnea and alterations in mental status, indicative of systemic dysfunction. Nausea may arise, potentially progressing to seizures or coma in severe cases. Thoracic discomfort or pressure may also be experienced, alongside

gastrointestinal disturbances such as nausea, vomiting, or diarrhoea, exacerbating the overall clinical presentation [16]. The fluid imbalance may occur, resulting in dehydration and decreased skin elasticity. Somnolence may occur, reflecting the systemic impact of renal dysfunction. Quantitative parameters like oliguria (urine output below 400 mL per day) or anuria (virtually absent urine output below 100 mL per day) serve as clinical indicators, although normoxia may also be observed in non-oliguric acute kidney injury cases. It's essential to recognize that AKI can manifest asymptomatically, necessitating vigilant medical evaluation for early detection and intervention to mitigate the risk of lasting renal impairment [17].

Biomarkers for Renal Disease:

Table 1 provides an overview of biomarkers associated with kidney function and damage, such as creatinine and BUN for functionality and KIM-1 and interleukin-18 for indicating damage, observed in both serum and urine specimens.

Sr. no.	Biomarker	Type of marker	Biological role	Source	Reference
	Creatinine	Functional	Creatinine is a metabolite generated in muscle tissue, derived from the high-energy product creatine.	Serum & Urine	[18-21]
	Blood urea Nitrogen	Functional	It is an end product of protein metabolism and is excreted by the kidneys	Serum	[22]
	Cystatin C	Functional	Produced by nucleated human cells; freely filtered	Plasma	[23]
	NAGL	Damage	Initially detected in neutrophil-gelatinase, and also induced in epithelial cells which experience inflammation	Plasma & Urine	[24]
	KIM-1	Damage	Type 1 memory glycoprotein is particular and sensitive, it is released in urine after tubular cell damage.	Urine	[25,26]
	Interleukin-18	Damage	Proinflammatory cytokine is released into urine following tubular damage.	Urine	[27,28]
	Netrin-1	Damage	Expressed in proximal tubular cells of a normal kidney released into urine after tubular cell damage.	Urine	[29,30]
	B2-microglobulin	Functional	It is a key protein in the immune system, contributing to the stability and expression of MHC class I molecules on cell surfaces, thus facilitating antigen presentation and maintaining immune homeostasis.	Serum & Urine	[31,32]
	Uric acid	Functional & Damage	Uric acid serves as an antioxidant and contributes to blood pressure regulation, but elevated levels are associated with kidney-related conditions such as nephrolithiasis, emphasizing its role as a potential biomarker for kidney health.	Serum	[33-36]
	Monocyte chemotactic	Functional & Damage	MCP-1 plays a pivotal role in kidney damage by orchestrating the recruitment of inflammatory cells to sites of renal injury, exacerbating tissue inflammation and contributing to the progression of kidney diseases.	Serum & Urine	[37,38]

Table 1: Biomarkers for Renal Disease

Creatinine: Creatinine, a byproduct of muscle metabolism, serves as a crucial biomarker for renal function assessment, commonly falling within the physiological range of 110-150ml/min for males and 100-130ml/min for females. The National Kidney Disease Education Program recommends utilizing serum creatinine levels to ascertain the GFR. Monitoring serum creatinine aids in tracking the progression of renal diseases; however, its interpretation is subject to influence by diverse factors including muscle mass, dietary patterns, and overall health status. Impaired kidney function can confound results due to heightened tubular secretion of creatinine [19]. Elevated creatinine levels are associated with conditions such as muscular dystrophy, anaemia, and hyperthyroidism, while reduced levels may be linked to glomerulonephritis and dehydration. Creatinine stands as the gold standard serum marker for AKI detection, owing to its affordability and chemical stability in clinical settings. Nevertheless, its utility is constrained by certain limitations. Traditionally, kidney function impairment is gauged through serum creatinine measurement, followed by GFR estimation using various mathematical models [20]. Creatinine clearance, a method involving blood and 24-hour urine collection, is determined using either the Jaffe

method or enzymatic tests. Stable kidney function is essential for the accurate application of estimating equations based on serum creatinine. Additionally, non-GFR determinants like dietary intake, muscle mass fluctuations, tubular secretion variability, and extrarenal creatinine excretion (particularly in advanced kidney disease) must be considered when interpreting creatinine levels. Variability in serum creatinine measurement further undermines the precision of these equations [21].Blood urea nitrogen: The diagnosis of AKI typically relies on assessing BUN and serum creatinine levels. However, these biomarkers may lack sensitivity and specificity in detecting AKI due to their susceptibility to various renal and non-renal factors that operate independently of kidney function. The production rate of urea, reflected in BUN levels, can fluctuate due to factors like dietary protein intake, tissue breakdown, or alterations in food supply. Although BUN levels rise with declining GFR, they are deemed less reliable than serum creatinine, as BUN can vary independently of GFR. Factors such as a high-protein diet or tissue damage can elevate BUN levels, whereas a very low-protein diet or liver failure may decrease BUN levels without affecting GFR. Thus, while BUN and serum creatinine are commonly used in diagnosing AKI, their interpretation must consider the diverse biological influences on these biomarkers. [22]. Cystatin C: Cystatin C, a cysteine-protease inhibitor with a molecular weight of 13.3 kD, has been proposed as a marker of renal function since 1985. It is produced at a constant rate by all nucleated cells, freely filtered in the renal glomeruli, and reabsorbed and catabolized in the proximal tubules, primarily by megalin. Studies have shown that cystatin C binds to megalin and cubilin with high affinity, and deficiencies in megalin have been associated with increased urinary excretion of cystatin C. In cases of ischemia/reperfusion injury, urinary cystatin C excretion increases, possibly due to a focal decrease in proximal tubule endocytosis. These findings have implications for clinical AKI management. Cystatin C offers advantages over other estimators of GFR, such as creatinine and urea, by avoiding confounding variables like muscle mass and protein intake. Studies comparing cystatin C- and creatinine-based prediction equations for estimated GFR (eGFR) suggest that cystatin C may be more precise, particularly in patients with measured GFR > 60 mL/min/1.73 m^2. However, despite its potential benefits, the cost of cystatin C assays remains a concern compared to creatinine. In specific populations with reduced muscle mass or degenerative muscle disease, cystatin C may provide more accurate information than serum creatinine. Additionally, cystatin C may have a role in assessing renal function in various clinical scenarios [23].

Neutrophil gelatinase-associated lipocalin: NGAL, a 25 kDa protein initially discovered bound to gelatinase in neutrophil-specific granules, plays a pivotal role in innate immunity against bacterial infections and is expressed by various immune cells, hepatocytes, and renal tubular cells during different disease states. Its proteolytic resistance enhances its potential as a clinical biomarker, primarily synthesized and secreted by tubular epithelial cells in renal segments. Normally, it is minimally detectable in plasma or urine but undergoes significant upregulation in acute tubular injury, making it a promising early indicator of kidney damage compared to traditional markers like creatinine. Studies suggest its involvement in iron transportation and demonstrate its renoprotective effects in ischemic injury. Animal studies and cell culture experiments have supported its early detection capability in kidney injury. NGAL has been extensively studied in AKI, particularly showing remarkable predictive performance in children post-cardiac surgery, with early elevation in urine and serum concentrations correlating strongly with AKI severity and duration. Similar predictive trends have been observed in adults undergoing cardiac surgery, albeit with more varied results likely due to confounding factors such as comorbidities. NGAL also shows promise as an early biomarker for AKI following contrast administration, especially in coronary angiography, and in critically ill patients in intensive care units. Additionally, it holds predictive value for contrast-induced nephropathy and other nephrotoxicity. In the context of kidney transplantation, NGAL levels in donors' urine serve as a potential indicator of delayed graft function. Despite some variability in predictive accuracy, NGAL emerges as a valuable tool for early detection and monitoring of AKI across diverse clinical scenarios in both paediatric and adult populations [24].

Kidney Injury Molecule-1: KIM-1 emerges as a promising biomarker for AKI and CKD due to several unique characteristics. Notably, KIM-1 is absent in healthy kidneys but prominently upregulated and inserted into the proximal tubule's apical membrane during injury, persisting until complete cell recovery. Its ectodomain undergoes rapid cleavage and remains stable at room temperature, facilitating its detection in urine. Current methods like blood urea nitrogen and creatinine measurements lack sensitivity and specificity, highlighting the need for better biomarkers in kidney assessment [25]. Animal studies demonstrate KIM-1's utility across various kidney insults, including ischemia, toxin exposure, and aging-related nephropathy. Human studies confirm its elevated expression in AKI and its correlation with disease severity and outcomes, even preceding traditional markers like serum creatinine. Moreover, KIM-1 shows promise in predicting graft loss in renal transplant recipients. Its specificity to kidney injury, superior sensitivity compared to conventional markers, and translational behaviour from animals to humans make it valuable for drug development and kidney safety monitoring. Regulatory bodies like the FDA and EMEA

recognize its significance in evaluating kidney damage. Ongoing research aims to explore KIM-1's role further in both acute and chronic kidney diseases, potentially paving the way for its use as a therapeutic target alongside its diagnostic utility [26].

Interleukin-18: IL-18 is a proinflammatory cytokine found naturally in the intercalated cells of the late distal convoluted tubule, connecting tubule, and collecting duct in healthy human kidneys. These cells contain the necessary components for releasing active IL-18, including pro-IL-18, P2X7, and caspase-1, which converts the preform of IL-18 into its active form. In conditions like AKI, IL-18 can be released into the urine [27]. Studies have shown that urine levels of IL-18 are significantly elevated in various renal diseases compared to healthy controls, with high sensitivity and specificity for diagnosing ATN Additionally, IL-18 levels in urine increase before serum creatinine levels in patients with AKI, particularly those with acute respiratory distress syndrome, predicting mortality. While early urine IL-18 measurements correlate with AKI severity and mortality, prospective analysis indicates it may not predict future AKI development reliably. However, IL-18's role as a proinflammatory cytokine in conditions like sepsis suggests its levels may be influenced by other factors such as endotoxemia and inflammatory diseases like arthritis and lupus. This broader influence on IL-18 levels may limit its specificity and sensitivity as a biomarker for AKI [28].

Netrin-1: Netrin-1, originally recognized as a neuronal guidance molecule, exhibits minimal expression in normal kidney tubular epithelial cells but becomes significantly upregulated and excreted in urine following AKI in animal models [29]. Studies have demonstrated a rapid increase in urinary Netrin-1 levels shortly after cardiac procedures such as cardiopulmonary bypass (CPB), peaking at 6 hours post-operation and remaining elevated for up to 48 hours, correlating with the severity and duration of AKI and hospital stay. Similar findings were observed in mouse models of ischemia-reperfusion injury, cisplatin toxicity, folic acid administration, and exposure to lipopolysaccharide, with urinary Netrin-1 levels spiking early, peaking at 6 hours, and declining thereafter. Notably, serum creatinine levels showed delayed elevation compared to Netrin-1, suggesting Netrin-1's potential as an earlier indicator of kidney injury. Human studies corroborate these findings, showing significant increases in urinary Netrin-1 levels in AKI patients compared to healthy controls across various aetiologies, including ischemic AKI, radiocontrast-induced AKI, sepsis-induced AKI, and drug-induced AKI. Sandwich enzyme-linked immunosorbent assay analysis further supports the notion of Netrin-1 as a universal biomarker for AKI detection. Overall, these findings suggest that urinary Netrin-1 serves as a promising early biomarker for renal injury, providing insights into diverse forms of AKI in both preclinical and clinical settings [30].

B2-microglobulin: Beta-2 microglobulin (B2M) is a protein integral to the human immune system, primarily found on nucleated cell surfaces and shed into bodily fluids, including blood, spinal fluid, and urine. In healthy kidneys, B2M is filtered by the glomeruli and reabsorbed by renal proximal tubules. Elevated B2M levels in urine indicate tubular dysfunction or damage, while elevated blood levels suggest glomerular dysfunction [31]. The B2M test is crucial in diagnosing kidney diseases, distinguishing between glomerular and tubular disorders, and monitoring conditions such as end-stage renal disease (ESRD) and dialysis-related amyloidosis (DRA). Additionally, it aids in detecting early kidney rejection post-transplant and assessing kidney function in individuals exposed to heavy metals. Elevated B2M levels are associated with an increased risk of cardiovascular disease (CVD) and mortality in kidney disease patients. Thus, B2M is a valuable biomarker, providing essential information for diagnosing renal disorders, evaluating prognosis, and monitoring kidney health in various clinical settings [32].

Uric acid: Elevated serum uric acid levels, resulting from the final oxidation product of purine metabolism, have long been associated with reduced GFR due to renal excretion. However, recent research suggests a more intricate role for uric acid in renal pathophysiology [33]. Studies indicate that hyperuricemia contributes to renal damage through various mechanisms, including endothelial dysfunction, arteriolar thickening, and impaired vasodilation, all of which exacerbate chronic CKD progression [34]. Research on both animal models and human subjects underscores the adverse effects of elevated uric acid levels on endothelial function. Endothelial dysfunction, characterized by impaired nitric oxide production and increased IL-6 synthesis, is a hallmark of hyperuricemia and is implicated in the progression of CKD [35]. Moreover, hyperuricemia correlates with hypertension, further complicating renal function and autoregulation. Furthermore, uric acid's interaction with fructose exacerbates renal damage, as evidenced by increased proximal tubular injury and inflammation. Fructose metabolism, particularly in the presence of elevated uric acid, leads to oxidative stress and chemokine release, contributing to nephropathy progression. Treatment strategies targeting uric acid levels, such as xanthine oxidase inhibitors like allopurinol, show promise in improving endothelial function and renal outcomes. However, the exact interplay between hyperuricemia, hypertension, and renal dysfunction remains complex and multifaceted [36].

Monocyte chemotactic peptide-1: Several years ago, research identified MCP-1 mRNA up-regulation in ischemia-reperfusion injury, suggesting its potential as a biomarker for the mononuclear inflammatory processes following ischemia-induced AKI. Subsequent studies demonstrated that MCP-1, a potent chemokine produced by renal cells, plays a pivotal role in acute ischemic and toxic kidney injury. To assess its utility, MCP-1 protein and mRNA were compared with NGAL in a mouse model representing intrarenal, prerenal, and postrenal injury. Results showed that MCP-1 levels increased significantly in intrarenal injury compared to NGAL, while prerenal and postrenal injury saw comparable increases in NGAL and MCP-1 gene expression [37]. Notably, uraemia alone induced NGAL gene expression but not MCP-1, suggesting MCP-1's potential specificity for AKI. Clinical studies further supported MCP-1's promise as a biomarker, observing distinct increases in urinary MCP-1 protein and mRNA levels in AKI patients without overlap in absolute urine levels. In summary, urinary MCP-1 shows potential as a useful biomarker for AKI, offering complementary information to NGAL analysis [38]. Electrolyte: CKD has emerged as a widespread health concern globally, with prevalence estimates ranging from 5-15%. CKD is associated with elevated risks of adverse cardiovascular events, progression to ESRD, and decreased life expectancy. The renal impairment characteristic of CKD disrupts the body's fluid, electrolyte, and acid-base balance, leading to complications such as hyperkalaemia, metabolic acidosis, and hyperphosphatemia. These disturbances contribute to muscle wasting, bone-mineral disorders, vascular calcification, and heightened mortality rates. While renal replacement therapies exist, current modalities have limitations. Notably, hyperkalaemia poses a significant risk, particularly in CKD and ESRD patients, with the potential for acute cardiac complications. Innovative medications like patiromer and ZS-9 offer promise in managing hyperkalaemia, particularly in individuals undergoing renin-angiotensin-aldosterone system (RAAS) inhibition [39]. Acidosis in CKD warrants close monitoring and intervention. Non-calcium-containing phosphorus binders show potential for improved cardiovascular outcomes. Ongoing research aims to elucidate pathogenic mechanisms and identify novel therapeutic targets. Sodium and magnesium imbalances, though briefly discussed here due to space constraints, also merit careful diagnosis and treatment due to their potential life-threatening consequences. Overall, electrolyte and acid-base disruptions play a crucial role in the pathophysiology of renal failure, emphasizing the need for comprehensive diagnosis and management strategies in CKD/ESRD care to optimize patient outcomes [40].

Proteinuria: Proteinuria, the presence of abnormal levels of protein in the urine, serves as an early indicator of various renal diseases, arising from damage to the glomerular apparatus or tubular dysfunction. Quantifying proteinuria aids in distinguishing between tubulointerstitial and glomerular pathologies, monitoring disease progression, and evaluating treatment responses. Typically, healthy adults excrete 20-150 mg of protein in urine over 24 hours, with proteinuria exceeding 3.5 grams per day indicative of nephrotic syndrome. While the conventional method involves 24-hour urine protein (24-hour UP) estimation, this approach has limitations, leading to sample discarding. Short-timed urine collections have been proposed as alternatives, assuming constant protein excretion throughout the day, although validation remains incomplete. Consequently, single-timed voided samples for 24-hour UP estimation have been explored, leveraging the constancy of urinary creatinine excretion relative to glomerular filtration rate. Studies have investigated the correlation between 24-hour UP and proteinuria estimated from spot protein/creatinine (PC) ratio across diverse patient groups. This study aims to establish the utility of the PC ratio in determining 24-hour urinary proteinuria in Indian patients with various renal disorders. Additionally, panels of protein measurements, including albumin and other markers, aid in the differential diagnosis. The prevalence of proteinuria in diabetic individuals underscores its significance in kidney disease. Haptoglobin clearance offers valuable diagnostic insights, especially when routine methods yield borderline results. In pregnancy, proteinuria assessment, typically through semi-quantitative dipstick urinalysis, plays a crucial role. Automated dipstick urinalysis emerges as a more accurate screening tool for proteinuria detection compared to visual testing, with confirmatory testing recommended through 24-hour urine collection or protein-creatinine ratio assessment [41].

CONCLUSION

Kidney damage results from a complex interplay of factors like infections, hypertension, diabetes, and toxins, leading to structural and functional impairments ranging from mild dysfunction to CKD or renal failure. Early detection and intervention are crucial, requiring a deep understanding of underlying pathophysiology and sophisticated diagnostic methods. Classification into prerenal, intrinsic, and postrenal causes aids in targeted treatment. Biomarkers like creatinine, blood urea nitrogen, cystatin C, and NGAL offer insights into renal function and injury progression. Electrolyte imbalances and proteinuria are important indicators. CKD's global impact is substantial, while AKI poses risks, particularly in hospitalized patients. Pathophysiology involves complex cellular and molecular mechanisms, including vascular, tubular, and inflammatory processes. Innovative diagnostics and therapies hold promise but require

further research. A multidisciplinary approach is essential for a better understanding of diagnosis managing kidney damage and improving patient outcomes.

ACKNOWLEDGMENT

I am grateful to the almighty for everything. I would like to express my gratitude to all those who have provided enthusiastic encouragement and useful critiques of my work. Lastly, but most importantly, I would like to thank my parents and family for their unwavering support and encouragement during my studies.

REFERENCES

1. Zhang WR, Parikh CR. (2019). Biomarkers of Acute and Chronic Kidney Disease. Annu. Rev. Physiol. 81: 309-333. https://doi.org/10.1146/annurev-physiol-020518-114605
2. Lopez-Giacoman S, Madero M. (2015). Biomarkers in chronic kidney disease, from kidney function to kidney damage. World. J. Nephrol. 4(1): 57-73. https://doi.org/10.5527/wjn.v4.i1.57.
3. Makris K, Spanou L. (2016). Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. Clin. Biochem. Rev. 37(2): 85-98. PMID: 28303073; PMCID: PMC5198510.
4. Moresco RN, Bochi GV, Stein CS, De Carvalho JAM, Cembranel BM, Bollick YS. (2018) Urinary kidney injury molecule-1 in renal disease. Clin. Chim. Acta. 487: 15-21. https://doi.org/10.1016/j.cca.2018.09.01.
5. Tögel F, Westenfelder C. (2014) Recent advances in the understanding of acute kidney injury. F1000Prime. Rep. 6: 83. https://doi.org/10.12703%2FP6-83.
6. Hamzic-Mehmedbasic A, Rebic D, Balavac M, Muslimovic A, Dzemidzic J. (2015) Clinical analysis of etiology, risk factors and outcome in patients with acute kidney injury. Mater. Socio. Med. 27(2): 70. https://doi.org/10.5455%2Fmsm.2015.27.71-74.
7. Selmi Y, Ariba YB, Labidi J. (2019) Epidemiology, diagnosis, and etiology of acute kidney injury in the elderly: A retrospective analysis. Saudi. J. Kidney. Dis. Transpl. 30(3): 678-685. https://doi.org/10.4103/1319-2442.261344.
8. Kovesdy CP. (2022) Epidemiology of chronic kidney disease: an update 2022. Kidney. Int. Suppl. 12(1): 7-11. https://doi.org/10.1016/j.kisu.2021.11.003.
9. Tejera D, Varela F, Acosta D, Figueroa S, Benencio S, Verdaguer C, Bertullo M, Verga F, Cancela M. (2017) Epidemiology of acute kidney injury and chronic kidney disease in the intensive care unit. Rev. Bras. Ter. Intensiva. 29: 444-452. https://doi.org/10.5935/0103-507x.20170061.
10. Priyamvada PS, Jayasurya R, Shankar V, Parameswaran S. (2018) Epidemiology and outcomes of acute kidney injury in critically ill: experience from a tertiary care center. Indian J. Nephrol. 28(6): 413-420. https://doi.org/10.4103%2Fijn.IJN_191_17.
11. Waikar SS, Liu KD, Chertow GM. (2008) Diagnosis, epidemiology and outcomes of acute kidney injury. Clin. J. Am. Soc. Nephrol. 3(3): 844-861. https://doi.org/10.2215/cjn.05191107.
12. Zappitelli M. (2008) Epidemiology and diagnosis of acute kidney injury. Semin. Nephrol. 28(5): 436-446. https://doi.org/10.1016/j.semnephrol.2008.05.003.
13. Wan L, Bagshaw SM, Langenberg C, Saotome T, May C, Bellomo R. (2008) Pathophysiology of septic acute kidney injury: what do we really know?. Crit. Care. Med. 36(4): 198-203. https://doi.org/10.1097/ccm.0b013e318168ccd5.
14. Gaut JP, Liapis H. (2021) Acute kidney injury pathology and pathophysiology: a retrospective review. Clin. Kidney. J. 14(2):526-536. https://doi.org/10.1093/ckj/sfaa14
15. Basile DP, Anderson MD, Sutton TA. (2012) Pathophysiology of acute kidney injury. Compr. Physiol. 2(2): 1303. https://doi.org/10.1002/cphy.c110041.
16. Roy JP, Devarajan P. (2020) Acute kidney injury: diagnosis and management. Indian. J. Pediatr. 87(8): 600-607. https://doi.org/10.1007/s12098-019-03096-y.
17. Nagamani R, Sudarsi K, Amaravati KS, Khan M, Sakuntala P, Deepthi D. (2015) A study on clinical profile of acute kidney injury. Int. J. Sci. Res. Publ. 5: 3-8.
18. McIlroy DR, Wagener G, Lee HT, Riou B. (2010) Biomarkers of acute kidney injury: an evolving domain. Anesthesiologists. 112(4): 998-1004. https://doi.org/10.1097/aln.0b013e3181cded3f.
19. Levey AS, Inker LA, Coresh J. (2014) GFR estimation: from physiology to public health. Am. J. Kidney. Dis. 63: 820–834. https://doi.org/10.1053/j.ajkd.2013.12.006.
20. Branten AJ, Vervoort G, Wetzels JF. (2005) Serum creatinine is a poor marker of GFR in nephrotic syndrome. Nephrol. Dial. Transplant. 20: 707–711. https://doi.org/10.1093/ndt/gfh719.
21. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. (2012) Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. Ann. Intern. Med. 156(11): 785-795. https://doi.org/10.7326/0003-4819-156-6-201203200-00391.
22. Dossetor JB. Creatininemia versus uremia. (1966) The relative significance of blood urea nitrogen and serum creatinine concentrations in azotemia. Ann. Intern. Med. 65: 1287–1299. https://doi.org/10.7326/0003-4819-65-6-1287.
23. Udupa, V, Prakash, V. (2019) Gentamicin-induced acute renal damage and its evaluation using urinary biomarkers in rats. Toxicol. Rep. 6: 91-99. https://doi.org/10.1016%2Fj.toxrep.2018.11.015.

24. Vaidya VS, Ferguson MA, Bonventre JV. (2008) Biomarkers of acute kidney injury. Annu. Rev. Pharmacol. Toxicol. 48: 463-493. https://doi.org/10.1146/annurev.pharmtox.48.113006.094615.
25. Yuexing Tu, Hui Wang, Renhua Sun, Yin Ni, Leilei Ma, Fei Xv. et al. (2014) Urinary netrin-1 and KIM-1 as early biomarkers for septic acute kidney injury. Ren. Fail. 36(10): 1559-1563. https://doi.org/10.3109/0886022X.2014.949764.
26. Pan HC, Yang SY, Chiou TT, Shiao CC, Wu CH, Huang CT. et al. (2022) Comparative accuracy of biomarkers for the prediction of hospital-acquired acute kidney injury: a systematic review and meta-analysis. Crit. Care. 26(1): 1-30. https://doi.org/10.1186/s13054-022-04223-6.
27. Lin X, Yuan J, Zhao Y, Zha Y. (2015) Urine interleukin-18 in prediction of acute kidney injury: a systemic review and meta-analysis. J. Nephrol. 28(1): 7-16. https://doi.org/10.1007%2Fs40620-014-0113-9.
28. Hirooka, Y., & Nozaki, Y. (2021) Interleukin-18 in Inflammatory Kidney Disease. Front. Med. 8: 639103. https://doi.org/10.3389/fmed.2021.639103.
29. Ramesh G, Krawczeski CD, Woo JG, Wang Y, Devarajan P. (2010) Urinary netrin-1 is an early predictive biomarker of acute kidney injury after cardiac surgery. Clin. J. Am. Soc. Nephrol. 5(3): 395-401. https://doi.org/10.2215/cjn.05140709.
30. Chew ST, Hwang NC. (2019) Acute kidney injury after cardiac surgery: a narrative review of the literature. J. Cardiothorac. Vasc. Anaesth. 33(4): 1122-1138. https://doi.org/10.1053/j.jvca.2018.08.003.
31. Mistry CD, O'Donoghue DJ, Nelson S, Gokal R, Ballardie FW. (1990) Kinetic and clinical studies of beta 2-microglobulin in continuous ambulatory peritoneal dialysis: influence of renal and enhanced peritoneal clearances using glucose polymer. Nephrol. Dial. Transplant. 5: 513–519. https://doi.org/10.1093/ndt/5.7.513.
32. M. Chonchol, M.G. Shlipak, R. Katz, et al. (2007) Relationship of uric acid with progression of kidney disease. Am. J. Kidney. Dis. 50(2): 239-247. https://doi.org/10.1053/j.ajkd.2007.05.013.
33. H.Y. Chang, C.W. Tung, P.H. Lee, et al. (2010) Hyperuricemia as an independent risk factor of chronic kidney disease in middle-aged and elderly population Am. J. Med. Sci. 339(6): 509-515. https://doi.org/10.1097/maj.0b013e3181db6e16.
34. D.I. Feig (2009) Uric acid: a novel mediator and marker of risk in chronic kidney disease. Curr. Opin. Nephrol. Hypertens. 18(6):526-530 https://doi.org/10.1097%2FMNH.0b013e328330d9d0.
35. Giordano C, Karasik O, King-Morris K, Asmar A. (2015) Uric Acid as a Marker of Kidney Disease: Review of the Current Literature. Dis. Markers. 382918. https://doi.org/10.1155/2015/382918.
36. Munshi R, Johnson A, Siew ED, Ikizler TA, Ware LB, Wurfel MM, Himmelfarb J, Zager RA. (2011) MCP-1 gene activation marks acute kidney injury. J. Am. Soc. Nephrol. 22(1):165-175. https://doi.org/10.1681/asn.2010060641.
37. Urbschat A, Obermuller N, Haferkamp A. (2011) Biomarkers of kidney injury. Biomarkers. 16: 22-30. https://doi.org/10.3109/1354750X.2011.587129.
38. Dhondup T, Qian Q. (2017). Acid-base and electrolyte disorders in patients with and without chronic kidney disease: an update. Kidney. Dis. 3(4): 136-148. https://doi.org/10.1159%2F000479968.
39. Dhondup T, Qian Q. (2017) Electrolyte and Acid-Base Disorders in Chronic Kidney Disease and End-Stage Kidney Failure. Blood. Purif. 43(1-3):179-188. https://doi.org/10.1159/000452725.
40. Zheng Y, Omar R, Zhang R, Tang N, Khatib M, Xu Q. et al. (2022) A wearable microneedle-based extended gate transistor for real-time detection of sodium in interstitial fluids. Adv. Mater. 34(10): 2108607. https://doi.org/10.1002/adma.202108607.
41. Heyman, S. N., Raz, I., Dwyer, J. P., Weinberg Sibony, R., Lewis, J. B., & Abassi, Z. (2021) Diabetic Proteinuria Revisited: Updated Physiologic Perspectives. Cells. 11(18): 2917. https://doi.org/10.3390%2Fcells1118291

CITATION OF THIS ARTICLE

Kunal Ravindra B,Aakansha Sanjaykumar M. Exploring Traditional and Novel Diagnostic Biomarkers for Renal Disease: A Comprehensive Review. Bull. Env.Pharmacol. Life Sci., Vol 13 [7] June 2024: 80-87