REVIEW ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

Recent Progress in Biomarker Detection in Cardiovascular and Renal Diseases

Upendra Prajapati*, Akash Yadav, Dinesh Kumar Jain

Abstract

Cardiorenal syndrome is a clinical condition in which there is a correlation between heart and kidney diseases. In recent times, many biomarkers have been studied in patients with cardiovascular diseases for developing proper knowledge of renal function and identifying patients who are more susceptible to chronic or acute deterioration of renal function. Because diagnostic and prognostic usefulness of a single time point biomarker is limited, biomarkers should be combined and monitored at multiple times for optimal clinical impact. This review mainly lays emphasis on the potential clinical uses of the biomarkers in cardiorenal syndrome, recent advancements of biomarkers in developing therapeutic agents for Alzheimer's disease, and classification of different types of biomarkers as well as highlights classic heart failure biomarkers with critical values adjusted to glomerular filtration rate and summarizes research progress of new heart failure biomarkers and future research directions.

Keywords: Biomarkers, Cardiorenal syndrome, Cardiovascular diseases, Heart and kidney diseases, Renal function

Asian Pac. J. Health Sci., (2023); DOI: 10.21276/apjhs.2023.10.2.04

Introduction

The term "cardiovascular diseases (CVDs)" refers to a broad range of conditions affecting the heart and blood arteries. Coronary heart disease, cerebrovascular illness, and rheumatic heart disease, among other ailments, are among the disorders that fall under the category of CVDs. These are the main reasons for deaths that are happening over the world. On average, CVDs are to cause for 17.9 million deaths annually. Heart attacks, strokes, and other conditions are the main causes of death. There are certain untimely deaths that affect people under the age of 70.[1]

Renal illnesses are situations where the kidneys cease to function and are unable to maintain the balance of the body's chemical composition or eliminate waste and excess water from the circulation. These include illnesses such as chronic kidney disease (CKD) and glomerulonephritis, among many others. Acute or chronic renal failure is the final outcome of these.[2] Globally, CKD is considered one of the major health issues. The prevalence of CKD is around 13.4% (11.7–15.1%) worldwide. Between 4.902 and 7.083 million people are expected to have end-stage kidney disease and require renal replacement treatment.[3]

Cardiovascular risk and chronic renal disease are the major causes of CVD, one of the leading causes of mortality. Kidney illness and CVD are closely related to one another, and any flaw in one organ might limit or improperly function in another, further leading to organ failure. According to reports, people with end-stage renal disease in general are more likely to die from CVD. Acute kidney injury (AKI) is the main factor contributing to the development of CVD, and it has been observed that treating and detecting AKI as soon as possible can help patients avoid the negative effects of CVD.[4]

A characteristic or biochemical agent known as a biomarker is frequently employed to quantify and evaluate a normal physiological or pathological process of pharmacological responses to a therapeutic treatment. Proteins, lipids, genomic, metabolomic, or proteomic patterns, imaging patterns, electric signals, and cells found on a urinalysis are a few examples.[5] In the field of medicine, these have attracted enormous scientific and clinical interest. They are used in early disease diagnosis, the prediction of patient outcomes, the identification of a patient's reaction to an intervention, and the evaluation of the effectiveness of the intervention. They are also used to predict the clinical efficacy and toxicity in pre-clinical research. The sensitivity and specificity for the identification and characterization of a specific disease condition will be improved with the use of a clinically useful biomarker.

Additionally, it is possible that some of these biomarkers will prove helpful for tracking the progress and severity of a particular disease.[6] It has been reported that a number of biomarkers can be used to detect kidney and cardiac disorders. Heart and renal illnesses are now widely understood to interact in complex ways. These two organs' pathogenesis is usually linked, and as a result, dysfunction in one commonly causes problems in the other. Several novel cardiac and renal biomarkers that help with the diagnosis, treatment, and prognosis of these diseases have recently been discovered. These typically serve as an addition to conventional biomarkers, which have a limited sensitivity and specificity.[5]

A biomarker is a measurable indicator of a disease state's presence or severity. It may be chemical, physical, or biological in nature, and the measurement may be cellular, molecular, functional, physiological, or biochemical.[7]

Department of Pharmacy, IPS Academy, College of Pharmacy, Indore, Madhya Pradesh, India.

Corresponding Author: Upendra prajapati, IPS Academy College of Pharmacy, Knowledge Village, Rajendra Nagar, A.B. Road, Indore - 452 012, Madhya Pradesh, India. E-mail 21prajapatiupendra2023@gmail.com

How to cite this article: Prajapati U, Yadav A, Jain DK. Recent Progress in Biomarker Detection in Cardiovascular and Renal Diseases. Asian Pac. J. Health Sci., 2023;10(2):2023;10(2):12-18.

Source of support: Nil.

Conflicts of interest: None.

Received: 01/05/2023 **Revised:** 12/05/2023 **Accepted:** 23/05/2023

Specific cells, molecules, genes, gene products, proteins, enzymes, other fluids, or hormones may be included. Biomarkers can also be complex organ functions or specific characteristic changes in biological structures.[8]

Several uses for biomarkers exist, such as tracking the progression of a disease, determining an appropriate treatment dosage schedule for a certain condition, and determining long-term vulnerability. They assist with prevention, early diagnosis, drug target identification, drug response, etc. There are numerous biomarkers for various diseases, including blood pressure, biomarkers including the P53 gene and MMPs for cancer, and serum LDL for cholesterol.[9]

The following is a classification of biomarkers:

Type 0, Type 1, and Type 2 biomarkers

This is a classification based on genetics and molecular biology methods.

Type 0 Biomarkers

Alternatively, these are referred to as natural history biomarkers.

They are used to correlate over time with clinical markers and to measure the disease' natural history. One type 0 biomarker used to analyze renal functions and look for associated damage is serum creatinine measurement.

Type 1 Biomarkers

They are drug activity biomarkers which help in indicating the effect of drug intervention. These are of three types:

i. Efficacy biomarkers – These are indicative of the therapeutic effects of a drug.
ii. Mechanism biomarkers – These aid in providing information about the mechanism of action of a drug.
iii. Toxicity biomarkers – These are indicative of toxicological effects of a drug.

Examples of type 1 biomarkers include blood glucose levels (efficacy biomarker), monitoring the effects of insulin treatment, and cytokines (mechanism biomarker) in various autoimmune disorders.

Type 2 Biomarker

These are surrogate markers, also known as surrogate endpoints, which are important in identifying the effects of a therapeutic treatment as well as serving as a substitute for a medical result of a condition. An example of a type 2 biomarker is cholesterol in heart disease. In this case, a higher level of cholesterol is associated with an increased risk of a variety of heart diseases, but this theory is not always relied upon because there are cases of patients who have quite high cholesterol levels but still do not develop any heart disease.[10]

Prognostic, Predictive, Pharmacodynamic, and Surrogate Endpoint Biomarkers

Prognostic Biomarkers

Prognostic in Greek means "foreknowing or foreseeing." These help in predicting the possible outcome of a disease in an untreated individual.

An example of a prognostic biomarker is the mutation status of *PIK3CA* in HER-2-positive metastatic breast cancer where individuals with mutated *PIK3CA* have been found to have lower rates of disease-free survival.

Predictive Biomarkers

The use of predictive biomarkers allows for the identification of individuals who are most likely to experience a positive clinical result in response to a particular treatment. These help to deliver a specific therapy to the patients for whom it is most likely to be helpful.

A therapeutic technique used to treat advanced non-small-cell lung cancer is erlotinib maintenance therapy. Progression-free survival after erlotinib therapy is considerably poorer in individuals with an EGFR mutation in the tumor than in patients who do not have an EGFR mutation. As a consequence, the presence of EGFR mutations serves as a biomarker for predicting erlotinib treatment response.[11]

Pharmacodynamic Biomarkers

The pharmacological effects of a drug can be determined with the use of these biomarkers, and this will ultimately inform if the treatment is operating as intended. As an illustration, PI3K inhibitors are utilized in the treatment of several malignancies. AKT is one of many downstream targets of the PI3K signaling pathway. AKT is phosphorylated when the PI3K pathway is activated, and phosphorylated AKT (pAKT) can serve as a pharmacodynamic biomarker to demonstrate that the PI3K pathway is being inhibited by Pi3K inhibitor therapy. A decrease in pAKT levels shows that the inhibitor is effective.[12]

Surrogate Biomarkers

Similarly to type 2 biomarkers, these. Blood pressure is an illustration of a substitute biomarker for cardiac disease. The clinical outcome should be effectively replaced by surrogate markers, and changes in the substitute should determine the clinical outcome. Surrogate biomarkers are only frequently used.[13]

Biomarkers of Exposure and Disease

Biomarkers of Exposure

They are commonly known as "Antecedent Biomarkers" which are used in risk prediction.

Biomarkers of Disease

These biomarkers are used for diagnosis and identifying the degree of progression of a disease.

Biomarkers can also be distinguished as drug related and disease related.[14]

Recent Progress in Biomarker Detection

It involves the following:

1. The development of therapeutic agents for Alzheimer's disease.
2. Predicting disease progression in polycystic kidney disease.

3. Novel immuno-oncology biomarkers for personalizing cancer therapy.
4. Identifying diagnostic and prognostic biomarkers for drug discovery of cystic fibrosis.
5. Detecting cardiovascular biomarkers to re-evaluate treatments for CVD.[15]

Characteristics of Biomarkers

According to the US Food and Drug Administration, an ideal biomarker must possess the following characteristics:

1. Specificity for a particular disease and it should have the ability of differentiating between different physiological states.
2. Safety while using and easy to measure.
3. Should be capable of faster diagnosis.
4. Economical.
5. Accurate.
6. Consistent between different ethnic groups and genders.[16]

Limitations of Biomarkers

Measurement Errors

Incorrect biomarker measurement will lead to variability and lower correlation of variables associated with the disease. Problems with the equipment used for taking samples or in transferring them to the laboratory may have an impact on how the biomarker is measured.

The determination of biomarkers may also be impacted by incorrect sample storage or modifications to the storage environment. Since technicians handle the majority of the specimens, proper training for new employees is essential. Well-organized procedure manuals that stress the specifics of paperwork, storage, specimen monitoring, and record-keeping may usually alleviate the majority of issues. In most laboratories and on a big scale, quality control and quality assurance processes are used to eliminate measurement errors.

Bias

The study of biomarkers can also involve bias. Complications occur when the presence of the biomarker is differentially related to either the disease or the exposure or when the specimen acquisition, storage, measurement, or ascertainment procedures differ to those with the disease in comparison to those without the disease or outcome of interest. High response rate from all cases and controls is needed to be maintained in order to reduce this bias and the investigators should have an objective review board review and they should monitor the conduct of the study, observing possible biases in subject participation or specimen ascertainment.

Cost

The choice of the biomarker for research is determined by the scientific question and the available funding. Cost is a constant concern. This may be important when considering about a tiny clinical trial; if thousands of people are used in an observational study, the cost might be rather large, even if the laboratory procedure is automated and simple. Depending on the sort of investigation, the researchers should be aware of the biomarker's false-positive or false-negative profile. No matter if it is a biomarker of exposure, susceptibility, or disease, "false positives" always result in additional work. "False negatives" frequently result in an increase in the study's overall cost. The amount of funding that is available is the only factor that determines tolerance for this problem.

Acceptability

The choice of biomarkers is not trivial owing to the source of biomarkers, which is either a human body tissue or body fluids. They can also be associated with some degree of risk. The patient will possibly benefit from the "new treatment" and the risk would be of a lesser concern in case of clinical trials. The source of the biomarker is crucial in quasi-experimental studies. Body fluids such as blood and urine are usually well tolerated. However, biopsy (particularly of neural tissue) and collection of cerebrospinal fluid are more difficult and associated with minor risks. Risk–benefit is a subject for the researcher to resolve. In order to convince institutional review boards that the study is safe and that the risk–benefit ratio favors advantages, pilot studies are always quite helpful.[15]

CVDs

CVDs are a class of diseases related to heart and blood vessels. These include coronary artery diseases (CAD) such as angina and myocardial infarction (commonly known as a heart attack). Others include stroke, heart failure, hypertensive heart disease, rheumatic heart disease, cardiomyopathy, abnormal heart rhythms, congenital heart disease, valvular heart disease, carditis, aortic aneurysms, peripheral artery disease, thromboembolic disease, and venous thrombosis. A variation in the underlying mechanisms is observed as per the intensity of the disease. Dietary risk factors are associated with 53% of CVD deaths.

Coronary artery disease, stroke, and peripheral artery disease involve atherosclerosis. This may be caused by high blood pressure, smoking, diabetes mellitus, lack of exercise, obesity, high blood cholesterol, poor diet, excessive alcohol consumption, and poor sleep, among other things. Hypertension is estimated to account for approximately 13% of CVD deaths, while tobacco is responsible for 9%, diabetes 6%, lack of exercise 6%, and obesity 5%.[17]

Renal Diseases

Nephropathy, often known as renal disease or kidney disease, is a medical term for kidney damage or kidney disease. There are various forms of nephritis, an inflammatory kidney disease, depending on where the inflammation is present. Blood tests can be used to diagnose inflammation. A non-inflammatory kidney condition is nephrosis. Nephrotic disorder and nephritic syndrome are conditions that can result from nephrosis and nephritis, respectively. Kidney disease typically results in a partial loss of renal function and can lead to kidney failure, which is the total loss of kidney function. The final stage of kidney disease, kidney failure, can only be treated with a transplant or dialysis.

Long-term kidney abnormalities (structural or functional in nature) that persist for more than 3 months are known as CKD. Acute renal injury, as it is now known, is characterized by a precipitous decline in kidney function over a period of 7 days. In 2007, almost one in eight Americans suffered from chronic renal

disease. This rate is rising with time, and as of 2021, it is estimated that 1 in 7 Americans will have CKD.[18]

Correlation between Cardiovascular and Renal Diseases

Patients having CVDs are usually found to have chronic or acute renal dysfunction. When patients with both acute and chronic heart failure (CHF) are taken into account, the prevalence of an altered renal function is thought to be much higher.

This connection results from the close relationship between both the heart and kidneys, which means that both organs have equal physiological and pathological states. The kidney controls fluid homeostasis, which is necessary for the heart to function, whereas hemodynamic, neurohormonal, inflammatory, and local mechanisms control blood perfusion, which is necessary for the kidneys to operate properly. Because of common risk factors (such as hypertension, diabetes, and atherosclerosis) and pathophysiological pathways, heart and kidney diseases commonly interact. In reality, both acute and chronic CVD and CKD are progressed by variables other than hemodynamic ones, including neurohormonal overactivity, endothelial dysfunction, inflammation, and oxidative stress. The phrase "cardiorenal syndrome" refers to the connection between cardiac and renal diseases and the potential for a mutual relationship on how they develop.

According to the organ that is primarily responsible for the development of the other, CRS has been further divided into five distinct kinds.

- Type 1 refers to AKI caused by acute cardiac disease.
- Type 2 refers to CKD caused by chronic heart disease.
- Type 3 refers to heart dysfunction caused by the acute worsening of kidney function.
- Type 4 refers to cardiac disease determined by CKD.
- Type 5 refers to a simultaneous injury of the heart and kidneys caused by systemic diseases.[19] Recent research has discovered that mild renal dysfunction, which produces common cardiovascular changes and ultimately predisposes to coronary heart disease as well as non-coronary cardiovascular issues, is also a significant cardiovascular risk factor. Patients with early renal dysfunction have been identified as having a wide range of different abnormalities (e.g., microalbuminuria and reduced estimated glomerular filtration rate [EGFR]).

Patients with early renal dysfunction have been discovered to have a number of traditional and novel cardiovascular risk factors, such as elevated asymmetric dimethyl-L-arginine concentrations, markers of microinflammation, oxidative stress, metabolic syndrome characteristics, abnormal adipokine concentrations, dyslipidemia, inappropriate renin–angiotensin system activation, and sympathetic overactivity.[20]

Kidney disease and heart dysfunction are related in a two-way manner. In reverse order, cardiac problems can cause progressive renal problems whereas renal problems can cause cardiac problems. In their study, van Dokkum *et al.* investigated how myocardial infarction affected the loss of renal function in rats with unilateral nephrectomies.

In animals with myocardial infarction, focal segmental sclerosis and proteinuria were found to be more severe, and a significant relationship between left ventricular pressures and proteinuria was discovered. According to the data, minor renal failure was made worse by heart injury, most likely due to neurohumoral signals. The connection between these two factors supports the idea of a "cardiorenal syndrome."[21]

Recently employed Biomarkers in Cardiorenal Diseases

The following section explains some of the recently used biomarkers for various cardiorenal diseases [Figure 1].

Renal Biomarkers in Chronic Kidney and CVDs

Through the use of equations used to calculate glomerular filtration rate (GFR), serum creatinine levels aid in the assessment of renal function. When serum creatinine linked to the muscle tissue breaks down, serum creatinine is produced. Its production rate is essentially constant, and the kidneys primarily eliminate it through glomerular filtration and just little through active tubular secretion. It has been shown that empirical formulas may quickly and accurately estimate GFR based on factors including age, gender, weight, and race as well as serum creatinine levels.

Similar to this, serum creatinine is evaluated in patients with CHF, particularly in those with normal or nearly normal renal function, to understand the physiology of the body in the diseased state.

Creatinine serum levels are not only used to estimate GFR but also to define the occurrence of worsening renal function (WRF). An increase of creatinine value >0.3 mg/dL and a decline in the stage of CKD associated with a 25% or greater drop in EGFR from baseline are the criteria indicated by the KDIGO guidelines to define the presence of a CKD progression.

Age, diet, gender, body mass, and race can also have an impact on the levels of creatinine in the serum. A decrease in creatinine levels based on muscle atrophy and cardiac cachexia can lead to an overestimation of GFR, which is akin to severe heart failure. Additionally, the greater filtration capacity of the remaining nephrons contributes to the decrease of GFR when a critical mass of nephrons is lost. Renal biomarkers should address two primary clinical needs in addition to GFR. They should enhance the estimation of renal function status and its degradation, as well as more precisely identify the pathophysiological factors that lead to acute or chronic WRF, which can also serve as a therapeutic target.[22]

Cystatin C

Cystatin C, a cysteine proteinase inhibitor, may be able to help overcome some of the challenges associated with estimating GFR from creatinine serum levels. All nucleated cells secrete it. In contrast to serum creatinine, it is freely filtered by the glomerulus, reabsorbed, and then not released by tubular cells. Age, body mass, nutritional state, and cachexia had little effect on the serum levels of cystatin C. When predicting early post-operative outcomes in advanced heart failure, that is, those who have received a left ventricular assist device, renal function by cystatin C is more accurately estimated when compared to serum creatinine. On the other side, some conditions including inflammation, thyroid dysfunction, obesity, and concurrent steroid treatment use may cause cystatin C levels to rise. Cystatin C has been shown to be effective in correctly classifying the risk of events in patients with HF (acute and chronic), as well as those with CAD (coronary artery disease), and the elderly. Due to its

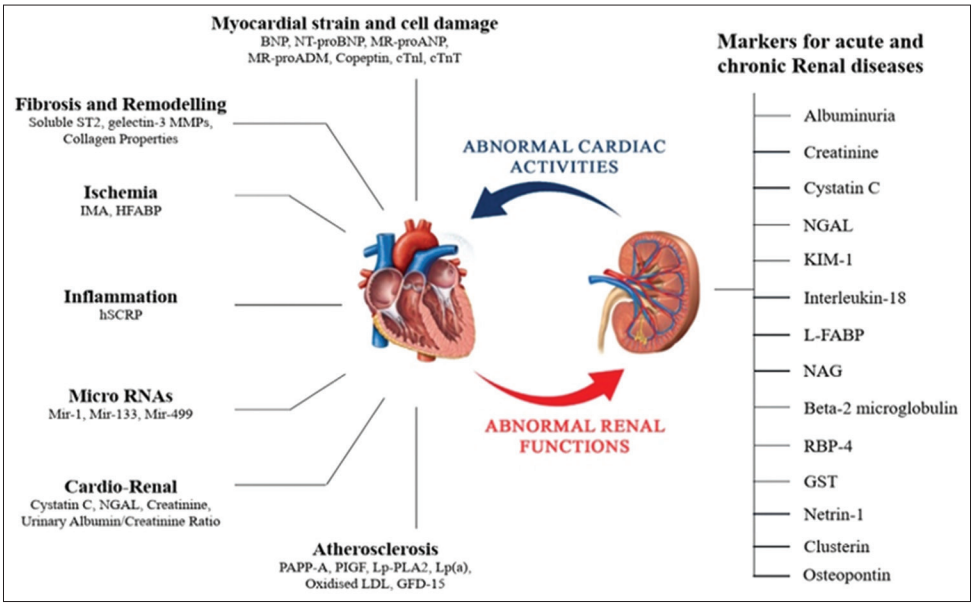

Figure 1: Renal biomarkers indicative of cardiorenal and renocardiac syndrome progression

higher cost compared to creatinine, the use of cystatin C is restricted in ordinary clinical care.[23]

Tubular Biomarkers

This evidence points to the emergence of renal impairment, especially in CHF patients. In cases of tubular damage, the proximal tubule's lysosomal protein N-acetyl-beta-glucosaminidase (NAG) is eliminated in the urine. The proximal tubule expresses a transmembrane glycoprotein, also known as a kidney damage molecule, as a result of hypoxic tubular injury. NAG and KIM1 serum levels in CHF patients irrespective of GFR indicate the level of risk of death or HF-related hospitalizations. Beta-2 macroglobulin (B2M), uromodulin, and alpha-1 macroglobulin (A1M) are other well-known biomarkers that are used. The liver produces the plasma protein A1M, which has antioxidant properties. Under normal conditions, only a small portion of B2M is discovered in the urine, but when the renal tubules are damaged, B2M concentrations rise. Tamm–Horsfall protein, also known as uromodulin, is a protein that can only be made by the kidney and is primarily found in healthy human urine. Although its exact role is unknown, experts believe that it controls ion transport, guards against infections, and prevents kidney damage and the development of kidney stones. CVD and death are associated with high levels of A1M and low amounts of uromodulin in the urine.[24]

Galectin-3 could be used to better understand the pathophysiological foundations of the underlying renal dysfunction and its progression in individuals with CVD. A beta-galactosidase-binding lectin known as Gal-3, which may be found both inside and outside of cells, is expressed in a wide range of organs and cell types. Its ability to induce fibrosis has been its primary pathologic function. Gal-3, which is produced by activated macrophages, stimulates collagen activation and deposition in the extracellular matrix as well as fibroblast proliferation. This behavior may start cardiac remodeling and eventually lead to heart failure.

Gal-3 has been shown to affect renal fibrosis and dysfunction in addition to its cardiac effects. Increased plasma levels of Gal-3 galectin-3 are likewise linked to a higher risk of incident CKD development in humans, but there is a correlation between Gal-3 levels and GFR in these creatures. In addition to being highly correlated with decreased GFR and microalbuminuria, higher levels of Gal-3 serum are also associated with a higher risk of renal function deterioration in patients with CHF.[25]

Renal Biomarkers in Cardiovascular Patients with AKI

Recently, the term AKI has taken the role of acute renal failure. It is defined as a rapid (within hours) reduction in kidney function and includes both harm (structural damage) and impairment (loss of function). AKI affects about 25% of people who are hospitalized for CVD (ranging from 15–30% of people with acute coronary syndrome (ACS) to 47% of people with acute decompensated heart failure). Dialysis is required by 20% of patients with AKI, 1% to 3% of patients with HF or ACS, and around 13% of patients with cardiogenic shock (AKI-D).

Neutrophil Gelatinase-associated Lipocalin (NGAL), NAG, KIM-1

A tiny protein called NGAL is completely reabsorbed in the proximal tubule after freely filtering through the glomerulus. It is produced by the kidney and other organs, and under typical circumstances, the amounts in the blood and urine are quite low. Similar to the other tubular indicators, when NGAL cannot be completely reabsorbed due to tubular injury, its urine levels rise and advance the rise in serum creatinine by 24 h. It has been found that NGAL is linked to the onset of poor renal function, which has a negative clinical outcome, in some HF patients. Patients with CVD have also been tested for NAG and KIM-1. NAG levels rise and are linked to a worse outcome in AKI patients. Another risk factor for AKI is NAG. KIM1 urine levels rise with a sensitivity in the identification of AKI, almost a day before the rise in serum creatinine.

In patients with acute heart failure, an increase in tubular

damage biomarkers, particularly urinary NGAL and KIM1, is predictive of the development of WRF and can help identify patients at higher risk of post-discharge mortality earlier, according to research by Cartin-Ceba *et al*.[26]

Fatty Acid-binding Proteins (FABPs)

Proteins called FABPs bind to free fatty acids. Heart-specific FABP (FABP-3) and liver-specific FABP (FABP-1) have been found to express themselves in the proximal and distal tubules of the kidney, respectively. AKI risk and ischemic tubular damage have been linked to urinary FABP-1 and FABP-3 levels. High FABP-3 readings are linked to a greater likelihood of cardiac disease in chronic HF patients.[27]

G1 Cell Cycle Arrest Biomarkers

AKI is influenced by a variety of intricate cellular and molecular processes connected to endothelium, epithelial, inflammatory, and interstitial cells. Cell cycle, immunology, inflammation, and apoptosis pathways are a few of these systems. TIMP-2 and insulin-like growth factor-binding protein-7 have recently been proposed as two urine indicators of cellular stress in the early stages of tubular cell injury (IGFBP7). These indications are the result of various insults (inflammation, ischemia, oxidative stress, drugs, toxins, and ultraviolet radiation).[28]

Cardiac Biomarkers in Kidney Diseases

For the diagnosis and prognosis of HF patients, the biomarkers brain natriuretic peptide (BNP) and peptide bond pro-BNP (NT-proBNP) are helpful. With respect to NT-proBNP in particular, renal function has an effect on these biomarkers' serum levels; the more severe the renal dysfunction, the greater the serum level. Even in CKD patients, natriuretic peptides are still linked to a worse prognosis. WRF and NT-pro BNP are linked in chronic HF.[29]

Biomarkers of Renocardiac Syndrome

The occurrence of structural and functional cardiac abnormalities up until the development of heart failure is determined with the help of ESRD. A high flow state brought on by arteriovenous fistulas and hemodynamic factors associated with fluid overload can encourage the eccentric remodeling of the left ventricle. A ventricular concentric remodeling, on the other hand, can be assisted by an increased afterload carried on by higher arterial systemic resistances and/or reduced arterial compliance. Non-hemodynamic factors such uremic toxins, oxidative stress, inflammatory, hyperparathyroidism, hypovitaminosis D, and hyperphosphatemia might worsen myocardial fibrosis.[30]

The gradual decline in the body's capacity to clear waste material from metabolic reactions and intestinal microbiota is what has led to an increase in uremic toxins. Patients with CKD have an entirely distinct intestinal microbiota than healthy subjects; this imbalance is known as "dysbiosis." The colon serves as an excretion organ when renal function declines. The proliferation of urease-positive species, which are in responsibility of converting urea into ammonia, occurs as a result of urea excretion, which raises the pH of the colon. Additionally, bacteria utilize amino acids for energy rather than anabolic functions, which leads to the production of uremic toxins such p-cresyl sulfate (PCS), indoxyl sulfate (IS), and trimethylamine N-oxide (TMAO). PCS and IS levels in CKD patients can be up to 100 times higher than in healthy persons. These substances cause oxidative stress, pro-fibrotic inflammation, and both renal and cardiovascular-related oxidative stress. Additionally, they have a propensity to encourage greater heart hypertrophy, which promotes cardiac dysfunction in ESRD. The connection between IS and PCS and a worse prognosis in patients with CVD and renal impairment supports their cardiovascular importance. Targeting these harmful substances could provide a treatment opportunity to slow the evolution of CRS.[31]

Conclusions

CKD is highly prevalent in those patients who are affected by CVD and HF. The most convenient way to assess overall kidney function in clinical practice is GFR estimation based on serum creatinine levels. In acute and chronic conditions, several limitations exist in the use of serum creatinine. New markers have been studied in order to overcome some of the drawbacks related to creatinine, to better assess the severity of renal dysfunction, to detect patients at higher risk of renal function worsening, and to more accurately identify patients prone to developing AKI. As a result, various novel biomarkers have been proposed in order to examine patients with end-stage renal diseases who are likely to experience deterioration of cardiac function. Future studies can help in understanding, the use of these biomarkers not only as prognostic markers but also as a basis or target for new therapeutic approaches.

References

1. Khan DT, editor. Cardiovascular Disorders. World Health Organization: World Health Organization; 2022.
2. Available from: www.niehs.nih.gov/health/topics/science/biomarkers/index.cfm [Last accessed on 2022 Dec 15]
3. Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. Adv Exp Med Biol 2019;1165:3-15.
4. Liu M, Li XC, Lu L, Cao Y, Sun RR, Chen S, *et al.* Cardiovascular disease and its relationship with chronic kidney disease. Eur Rev Med Pharmacol Sci 2014;18:2918-26.
5. Vaidya VS, Bonventre JV, editors. Biomarkers: In Medicine, Drug Discovery, and Environmental Health. United States: John Wiley and Sons; 2010.
6. Parikh NI, Vasan RS. Assessing the clinical utility of biomarkers in medicine. Biomark Med 2007;1:419-36.
7. World Health Organization. WHO international programme on chemical safety. In: Biomarkers and Risk Assessment: Concepts and Principles. Geneva: World Health Organization; 1993.
8. Goffredo G, Barone R, Di Terlizzi V, Correale M, Brunetti ND, Iacoviello M. Biomarkers in cardiorenal syndrome. J Clin Med 2021;10:3433.
9. Drain PK, Hyle EP, Noubary F, Freedberg KA, Wilson D, Bishai WR, *et al*. Diagnostic point-of-care tests in resource-limited settings. Lancet Infect Dis 2014;14:239-249.
10. Kaplan JM, Wong HR. Biomarker discovery and development in pediatric critical care medicine. Pediatr Crit Care Med 2011;12:165-73.
11. Seo Y, Park YH, Ahn JS, Im YH, Nam SJ, Cho SY, *et al.* PIK3CA mutations and neoadjuvant therapy outcome in patients with human epidermal growth factor receptor 2-positive breast cancer: A sequential analysis. J Breast Cancer 2018;21:382-90.
12. Yang J, Nie J, Ma X, Wei Y, Peng Y, Wei X. Targeting PI3K in cancer: Mechanisms and advances in clinical trials. Mol Cancer 2019;18:26.
13. Fleming TR, DeMets DL. Surrogate end points in clinical trials: Are we being misled? Ann Intern Med 1996;125:605-13.
14. Mayeux R. Biomarkers: Potential uses and limitations. NeuroRx

2004;1:182-8.
15. Pal M and Bandyopadhyay S. Biomarkers in Overactive Bladder. Kolabtree Blog 2020.pp 266-272.
16. Sahu P, Pinkalwar N, Dubey RD, Paroha S, Chatterjee S, Chatterjee T. Biomarkers: An emerging tool for diagnosis of a disease and drug development. Asian J Res Pharm Sci 2011;1:9-16.
17. Mendis S, Puska P, Norrving BE, World Health Organization. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: World Health Organization; 2011.
18. Kim KH, Lee MS, Kim TH, Kang JW, Choi TY, Lee JD. Acupuncture and related interventions for symptoms of chronic kidney disease. Cochrane Database Syst Rev 2016;2016:CD009440.
19. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol 2008;52:1527-39.
20. Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. N Engl J Med 1974;290:697-701.
21. van Dokkum RP, Eijkelkamp WB, Kluppel AC, Henning RH, van Goor H, Citgez M, *et al*. Myocardial infarction enhances progressive renal damage in an experimental model for cardio-renal interaction. J Am Soc Nephrol 2004;15:3103-10.
22. Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, *et al*. Comparative performance of the CKD epidemiology collaboration (CKD-EPI) and the modification of diet in renal disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis 2010;56:486-95.
23. Newman DJ, Thakkar H, Edwards RG, Wilkie M, White T, Grubb AO, *et al*. Serum cystatin C measured by automated immunoassay: A more sensitive marker of changes in GFR than serum creatinine. Kidney Int 1995;47:312-8.
24. Garimella PS, Lee AK, Ambrosius WT, Bhatt U, Cheung AK, Chonchol M, *et al*. Markers of kidney tubule function and risk of cardiovascular disease events and mortality in the SPRINT trial. Eur Heart J 2019;40:3486-93.
25. Rubinstein N, Ilarregui JM, Toscano MA, Rabinovich GA. The role of galectins in the initiation, amplification and resolution of the inflammatory response. Tissue Antigens 2004;64:1-12.
26. Cartin-Ceba R, Kashiouris M, Plataki M, Kor DJ, Gajic O, Casey ET. Risk factors for development of acute kidney injury in critically ill patients: A systematic review and meta-analysis of observational studies. Crit Care Res Pract 2012;2012:691013.
27. Noiri E, Doi K, Negishi K, Tanaka T, Hamasaki Y, Fujita T, *et al*. Urinary fatty acid-binding protein 1: An early predictive biomarker of kidney injury. Am J Physiol Renal Physiol 2009;296:F669-79.
28. Yang QH, Liu DW, Long Y, Liu HZ, Chai WZ, Wang XT. Acute renal failure during sepsis: Potential role of cell cycle regulation. J Infect 2009;58:459-64.
29. Maisel AS, Katz N, Hillege HL, Shaw A, Zanco P, Bellomo R, *et al*. Biomarkers in kidney and heart disease. Nephrol Dial Transplant 2011;26:62-74.
30. Granata A, Clementi A, Virzì GM, Brocca A, de Cal M, Scarfia VR, *et al*. Cardiorenal syndrome type 4: From chronic kidney disease to cardiovascular impairment. Eur J Intern Med 2016;30:1-6.
31. Lin CJ, Wu V, Wu PC, Wu CJ. Meta-analysis of the associations of p-cresyl sulfate (PCS) and indoxyl sulfate (IS) with cardiovascular events and all-cause mortality in patients with chronic renal failure. PLoS One 2015;10:e0132589.