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Different Biomarkers of Acute kidney Injury in Cancer Patients

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Abstract
Acute Kidney Injury (AKI) occurs if the kidneys suddenly lose their ability to remove waste products. When the kidneys lose their ability to filter, dangerous levels of waste products can accumulate, which can upset the chemical composition of the blood and urine. Chemotherapy is one of the methods used to treat or temporarily reduce cancer by using certain medications. The main task of this treatment is to kill cancer cells without seriously damaging the surrounding tissues. However, this type of treatment also has destructive effects on healthy cells and tissues in the body. Researchers studying cancer patients undergoing chemotherapy found that people undergoing this type of treatment may develop serious kidney problems and be forced to use treatments such as dialysis and kidney transplants. Research showed that people with more severe cancers and advanced tumors are more likely to have acute kidney injury than those with early-stage cancer. AKI biomarkers can be selected from the patient's serum, urine, or body imaging components. Various studies showed that urine is a source of the best markers in AKI. Biomarkers in plasma and urine, such as N-acetyl-β-glucosaminidase, Cystatin-C, β2-microglobulin , Cysteine-Rich Protein, Osteopontin, Fetuin-A, Kidney Injury Molecule-1, Liver-type fatty acid-binding protein, Netrin-1, Neutrophil gelatinase-associated lipocalin, and interleukin-18 are effective tools for early detection of AKI. In this review study, an attempt was made to collect biomarkers related to AKI disease.
Keywords: Acute kidney injury, Chemotherapy, Cancer

Introduction

Cancer is the second most common cause of premature death in children. Children may experience a variety of complications during their illness, including kidney damage (1). One of the most common renal complications in these children is acute kidney injury (AKI) (2). AKI-related risk factors in cancer patients can lead to tumor infiltration and tumor lysis syndrome. Increased complications with therapeutic drugs can have adverse effects on cancer and cancer prognosis (3). However, the complications are also dependent on the type of cancer (4-6), and it should not be overlooked that children's response to cancer can be quite different from that of adults (4,5). Other studies have shown that urinary tract cancers in children increase the risk of developing AKI and associated hospitalization and mortality rates in these patients (4). Medical development is of particular importance for measuring the incidence of AKI using biological criteria in pediatric cancer patients (7). Furthermore, there is an essential requirement for biomarkers to diagnose the disease early, predict the severity of the injury, and evaluate safety during drug production (8, 9). These biomarkers can be expressed at different levels such as cellular, molecular, demographic, and even ecosystem depending on their type and characteristics. Therefore, we assessed different biomarkers of acute kidney injury in cancer patients. In this regard, AKI,

biomarkers, and specific biomarkers of AKI were assessed in detail in text.

AKI

Acute Kidney Injury (AKI) is known as a clinical disorder with acute renal failure (10). This disorder is caused by sudden failure or a decrease in kidney function, which increases the amount of toxin excreted by the kidneys in the blood (11). The range of clinical symptoms of this disease can be very wide and in most of these patients, dialysis is required (11). The results of clinical and laboratory studies indicated the existence of functional and structural abnormalities with a series of markers of kidney damage, including blood, urine, creatinine, etc. It can cause fatal problems (12). Kidney failure is of two types. Various factors can cause acute renal failure, which can be divided into three categories: pre-renal causes (insufficient blood supply to the kidneys, for example, due to severe renal artery stenosis), renal causes (such as glomerulonephritis and acute tubular necrosis), and post-renal causes (such as urinary tract obstruction, for example, due to kidney stones or benign prostatic hyperplasia) (10, 14). The main symptoms of this problem are a sharp decrease in urine volume and an increase in blood urea and creatinine levels (14). Kidney disease has the same treatment when it comes to the final stages of severe failure, regardless of what causes the failure or whether it is acute or chronic (15). The principles of treatment are diet, taking some supplements, kidney transplantation, and hemodialysis or peritoneal dialysis (16).

Acute kidney damage has three causes:

A severe and sudden drop in blood flow to the kidneys: Excessive blood loss, injury, or severe infections called sepsis can reduce blood flow to the kidneys.

Insufficient fluid volume in the body (water loss): It can also damage the kidneys.

Damage caused by certain drugs, toxins, or infections: Most of the drugs are those used in chemotherapy (8). Another important factor is the use of X-rays. Most people do not have any kidney problems due to medication. But people with serious, long-term health problems are more likely to have kidney problems than others. There is an essential requirement for better biomarkers to diagnose the disease early, predict the severity of the injury, and evaluate safety during drug production (8, 9).

Biomarkers

A biomarker is measurable indicator of certain biological conditions (17). Sometimes, it also refers to a substance whose shows a living organism. Biomarkers are often evaluated in the study of natural biological and pathogenic processes, or drug responses to a particular treatment, and are used in many disciplines (18). In general, a biomedical marker refers to anything that can be used as an indicator of a particular disease or certain physical condition of an organism (19). Biomarkers can be expressed at different levels such as cellular, molecular, demographic, and even ecosystem depending on their type and characteristics. According to studies, biomarkers can be divided into two types, and this division is based on the applications and responses that living organisms have to anti-life substances. Usually, the concentrations of some contaminants in the study environment are much lower than the detection limits of existing laboratory measuring instruments (20). Therefore, without observing contamination, the effects of these substances on living components can be detected. Based on their diversity and application, these indicators can be effective in this evaluation, and the salient features that can make them a monitoring tool in various sciences are their specificity, sensitivity, and practicality. Such a marker can be used as a tool to check the health of an organ or other aspects of a living organism (21). There is

an essential need for better biomarkers to diagnose the disease early, predict the severity of the injury, and evaluate safety during drug production (20). These biomarkers can help drug makers make more informed decisions about the type of product to advance the trial, the dosage of the test, as well as how to design clinical trials, which clearly provide information about the benefits and safety of the product. AKI biomarkers can be selected from the patient's serum, urine, or body imaging components (22). According to various studies, urine is known as a source of the best markers for AKI and the way forward in the use of urinary biomarkers in AKI disease as a useful tool for early detection, identification of the mechanism of injury, location assessment, and severity of the injury is clear (23). Therefore, it is hoped that such biomarkers, alone or in combination, will be useful in facilitating early detection and monitoring the progression and elimination of AKI (24).

- **Neutrophil Gelatinase-Associated Lipocalin (NGAL)**

Lipocalins are binding proteins that allow these molecules to carry lipophilic molecules. NGAL is a lipocalin produced by neutrophils in response to injury, infection, cancer, and kidney damage. This protein is involved in cellular processes including proliferation, differentiation, and apoptosis. NGLA is usually elevated in physiological processes, such as ischemic and nephrotoxic, within hours of injury in urine and plasma. Studies have shown a direct link between this factor and the need for dialysis and mortality. Research on acute or chronic clinical kidney problems in children has found this protein to be a very promising biomarker in early diagnosis (25-27).

- **Interleukin-18 (IL-18)**

IL-18, an anti-inflammatory cytokine that is initially synthesized passively (24 kDa) and subsequently is activated by caspase-1. This cytokine is produced systematically in renal tubular epithelial cells in people with AKI, 5-6 hours after urinary incontinence. In patients with acute tubular necrosis, the mean concentration of IL-18 was higher than in other patients. According to studies, the urinary concentration of IL-18 peaks as the condition of patients with AKI worsens. Compared to other biomarkers, this marker is not considered a strong primary predictor (28, 29). There may be many non-specific biomarkers of AKI; however, we explain biomarkers of AKI.

Biomarkers of AKI

Biomarkers that can be used for AKI can be in serum, urine, or other quantitative components, or even imaging tests. However, among the available components, urinary components are usually the best biomarkers for early diagnosis of AKI. In addition to the efficiency of these biomarkers in the early diagnosis of AKI, they can identify the mechanism of the injury, assess the location of the injury, and assess the severity of the injury. However, efforts are being made to ensure that one or a combination of these biomarkers can help achieve these goals. The following are the biomarkers available for AKI (30, 31).

- **N-acetyl-β-glucosaminidase (NAG)**

NAG is a lysosomal enzyme present in the proximal region of the kidney. This enzyme is sensitive to damage to the proximal renal region. Studies have shown that urinary NAG levels in patients increase within 12 hours to 4 days before elevated serum creatinine. The higher the concentration of urinary NAG in AKI patients, the higher the risk of dialysis and death in these patients. In general, two advantages of using this biomarker in AKI patients are simple and reproducible enzyme assay and the other is the high sensitivity of this biomarker for proximal renal lesions. But the main disadvantage of this biomarker is its inhibition by some

toxins and heavy metals in the urine (32-34).

- **β2-microglobulin (β2M)**

β2M is a light chain-forming protein of the major tissue compatibility molecule I, which is expressed on the cell surface of all nucleated cells (35). In regulating cellular circulation, this molecule separates from the heavy chain and enters the bloodstream as a monomer, which is eventually filtered by the glomerulus and almost completely reabsorbed and catabolized by proximal tubular cells. In AKI, this process is disrupted and the β2M molecule is excreted in the urine. Increased urinary excretion of β2M can be used as a biomarker before the onset of serum creatinine about 4 to 5 days after renal injury. But the main problem with this biomarker is that it is very sensitive to environmental conditions such as room temperature and pH (17, 36).

- **Liver-Type Fatty Acid-Binding Protein (L-FABP)**

Proximal renal tubular cells contain the L-FABP protein, which binds fatty acids to the liver and aids in the transport and metabolism of fatty acids. The expression of this protein is increased during tissue damage or disorders such as AKI. Studies have identified this biomarker as one of the best early prognostic biomarkers, appearing in the urine within minutes to hours (37, 38).

- **Netrin-1**

Netrin-1 is a molecule similar to laminin that is expressed in many organs, including the kidneys. Urinary excretion of this protein increases in the urine after kidney damage, including AKI. Netrin-1 is an early indicator of AKI. This biomarker is valuable in this regard because one of the problems with AKI in hospitalized patients is that it is diagnosed late and this is one of the leading causes of death in these patients. This biomarker, except for its premature appearance in urine, has high sensitivity and specificity in kidney damage (39, 40).

- **Cystatin-C (Cys-C)**

Cys-C is a 13 kDa protein that is one of the most important inhibitors of extracellular cysteine proteases (41). The serum concentration of this biomarker is not dependent on factors such as sex, age, and muscle mass. This marker can be considered as a sensitive serum marker for AKI and cardiovascular damage. Cys-C has long been used as a useful marker in the progression of kidney disease, especially in diabetics, although urinary levels of this marker have recently been measured using diagnostic kits (42).

- **Cysteine-Rich Protein (Cyr61)**

Cyr61 is a heparin-bound protein that is secreted and linked to the cell surface and extracellular matrix. Cyr61 is a ligand for integrin and regulates angiogenesis and tumorigenesis through integrin receptors such as αvβ3, αvβ5, and α6β1 (43). Cyr61 develops rapidly in the proximal tubules of the kidney three hours after renal injury. It is also excreted in the urine within three to six hours and is considered a potential biomarker for AKI [44]. One of its disadvantages is the decrease in serum level in urine over time and the other is the immunoblotting method to evaluate this marker in urine, which is considered insensitive to evaluate this marker (30).

- **Osteopontin (OPN)**

OPN is known as bone phosphoprotein. It is highly expressed in some tissues, such as bone, kidney, and optic tissue, and data suggest that this phosphoprotein is more expressed in the kidneys of humans and mice (46). OPN is associated with several functions, such as regulating osteoclast function during bone formation, tumorigenesis and deformation, and macrophage accumulation. OPN is associated with inflammation and fibrosis, and glomerulonephritis. A commercial ELISA kit is available to quantify OPN in human urine, designed for quantitative and early detection of AKI (46, 47).

- **Fatty Acid Binding Protein** (FABPs)

FABPs are small cytoplasmic proteins (15 kDa) found in tissues that are active in

fatty acid metabolism. In the human kidney, two types of FABP are found, including hepatic FABP (L-FABP) in the proximal and cardiac FABP (H-FABP) in the distal [48]. FFA is a potential biomarker for several pathological conditions and diabetic nephropathy. Although L-FAPB is an attractive biomarker for various kidney diseases, it does not appear to be sufficient to determine the differentiation of AKI from other renal impairments alone to determine the use of L-FABP in AKI (37, 38, 49).

- **Sodium/Hydrogen Exchanger Isoform (NHE3)**

NHE3 is the most plentiful sodium transporter in tubules of kidney. McKay et al. showed that NHE3 was easily detected in the urine of healthy mice. A previous study has confirmed the presence of NHE3 in the urinary exosome of AKI patients (48). The immune system performed a semi-adjuvant on a fraction of the urinary membrane and diagnosed NHE-3 as a suitable marker in differentiating between control patients, patients with prenatal azotemia, patients with acute glomerulus, and patients with ischemic/nephrotoxic acute tubular necrosis. (17, 32).

- **Fetuin-A**

Fetuin is an acute-phase protein that is synthesized in the liver and secreted into the bloodstream (50). This protein stimulates bone resorption, regulates insulin activity and liver growth activity, and responds to inflammation and inhibition (30). In kidney damage, urine shows an increase of Fetuin-A more than 50 times in 2 days. According to studies, urinary Fetuin-A was much higher in patients admitted to the intensive care unit than in patients without AKI admitted to the intensive care unit and healthy volunteers (50). Although the function of fetuin-A in AKI patients is unknown, it may play a role in renal cell apoptosis. The test method is usually immunoblotting, which is a semi-qualitative method and does not have high sensitivity. Measuring this biomarker, on the other hand, requires isolation and verification of exosomes is a time-consuming process (50).

- **Kidney Injury Molecule-1 (KIM-1)**

KIM-1 is a glycoprotein involved in cell-to-cell or cell-to-cell matrix attachments that is normally present in small amounts in the kidney, but in physiological conditions, such as AKI, ischemia, or damage to the proximal renal tubules, is in high levels, and is highly regulated in the proximal tubules after ischemic or toxic AKI. With AKI, this protein is released in the urine by proteolytic enzymes. This protein has also been found in other diseases such as polycystic kidney disease, kidney damage, and proteinuria. As a result, it does not have the high prognostic properties of AKI (51-54).

Conclusion

AKI is a common and devastating disease that can result from the side effects of chemotherapy in cancer patients. Attempts to identify biomarkers to aid in early detection have led to the identification of a number of urinary and serum markers, and studies have shown that urinary markers are a priority because, at the time of admission, they can independently show the development of AKI earlier than serum creatinine; therefore, the use of these markers allows rapid diagnosis and quantification. Biomarkers have the potential to change the way patients with AKI are diagnosed and treated.

Conflicts of interest

There are no conflicts of interest.

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