

Renal Pathophysiology and Nephrotoxicity: Renal Biomarkers' Importance and Function in the Early Diagnosis of Acute Renal Damage

Abstract

Nephrotoxicity is defined as a fast decline in kidney function brought on by the toxic effects of drugs and substances. There are several types, and some medications may have multiple negative effects on renal function. Nephrotoxic compounds are known as nephrotoxins. Nephrotoxicity is caused by a number of different factors, such as renal tubular toxicity, inflammation, glomerular injury, crystal nephropathy, and thrombotic microangiopathy. Blood urea and serum creatinine, the conventional indicators of nephrotoxicity and renal dysfunction, are viewed as being insufficiently sensitive indicators of early renal injury. Therefore, novel biomarkers that are more sensitive and highly specific and that provide information on the location of underlying renal injury were needed for the diagnosis of the early renal injuries. Blood urea and serum creatinine are less sensitive than Kidney Injury Molecule-1, Cystatin C, and neutrophil gelatinase-associated lipocalin serum levels in the diagnosis of acute kidney injury during nephrotoxicity [1].

The nephron, the kidney's fundamental functional unit, is made up of many cell types that are arranged into the kidney. Any stimulus that causes the death of these cells has the potential to harm or even kill off the kidneys. Renal failure may have inherent or extrinsic causes. Heart disease, obesity, diabetes, sepsis, and liver and lung failure are examples of extrinsic causes. Glomerular nephritis, polycystic kidney disease, renal fibrosis, tubular cell death, and stones are a few examples of intrinsic causes. The kidney is important in regulating the toxicity of many medications, contaminants from the environment, and natural chemicals. There are a number of cancer therapies, illicit substances, antibiotics, and radiocontrast agents that are known to be nephrotoxic. Cadmium, mercury, arsenic, lead, trichloroethylene, bromate, brominated-flame retardants, diglycolic acid, and ethylene glycol are environmental contaminants that have been linked to kidney damage. Aristolochic acids and mycotoxins like ochratoxin, fumonisin B1, and citrinin are examples of naturally occurring nephrotoxicants. Mechanisms of renal failure brought on by nephrotoxicants and extrinsic factors have a number of traits. The molecular pathways regulating renal cell death share many commonalities, which is the main reason for this shared ground. The present state of the study of nephrotoxicity is outlined in this review. The emphasis is on fusing pathologically caused renal failure with our understanding of nephrotoxicity. Such methods are required to address important issues in the area, such as the development from acute kidney damage to chronic kidney disease and the diagnosis, prognosis, and treatment of both acute and chronic renal failure [2].

Keywords: Cystatin C • glomerular damage • nephrotoxicity • kidney • renal pathology • acute kidney injury • chronic kidney disease • renal failure

Introduction

The kidney is the primary organ needed by

the human body to achieve and carry out several crucial processes, such as

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Received: 01-Oct-2022, Manuscript No. OAIN-22-77370; **Editor assigned:** 03-Oct-2022, PreQC No. OAIN-22-77370 (PQ); **Reviewed:** 17-Oct-2022, QC No. OAIN-22-77370; **Revised:** 22-Oct-2022, Manuscript No. OAIN-22-77370 (R); **Published:** 29-Oct-2022; DOI: 10.47532/oain.2022.5(5).53-57

detoxification, extracellular fluid management, homeostasis, and the excretion of harmful compounds. Nephrotoxicity is defined as a fast decline in kidney function brought on by the toxic effects of drugs and substances. There are several types, and some medications may have multiple negative effects on renal function. Nephrotoxic compounds are known as nephrotoxins. Nephrotoxicity should not be confused with the fact that some drugs need to have their dose adjusted for the diminished renal function since they excrete mostly through the kidneys (e.g., heparin). Most medications have a more severe nephrotoxic impact on those who already have renal failure. Drugs are responsible for around 20% of nephrotoxicity; in the elderly, when life expectancy has increased and medication adherence is higher, this number has increased. Because aminoglycosides are endocytosed and accumulated specifically in the proximal tubule epithelial cells through the multi-ligand receptor megalin, aminoglycosides can induce nephrotoxicity. Recently, a consensual list of phenotypic standards for inducing nephrotoxicity was released. In observational studies, novel renal biomarkers, in particular kidney injury molecule-1, have showed promise in their ability to detect proximal tubular damage sooner than conventional markers. To guide translation into clinical practise, more research must show a clear link with clinically relevant outcomes [3].

The detrimental effect of chemicals on renal function is known as nephrotoxicity. Molds and fungus, cancer treatments like cisplatin, antibiotics like aminoglycosides, metals like mercury, arsenic, and lead, as well as illicit narcotics like cocaine are some examples of these substances. Changes in renal function as measured by the glomerular filtration rate (GFR), blood urea nitrogen (BUN), serum creatinine (sCr), or urine output are one sign of nephrotoxicity; however, nephrotoxins can cause kidney damage without altering any recognised clinical marker of renal function. According to research, proximal tubule necrosis in male Sprague Dawley rats exposed to gentamicin can reach up to 75% before BUN or sCr levels rise. There is a relatively complex staging approach for the evaluation of renal damage. When comparing acute kidney injury (AKI) with chronic kidney disease (CKD), time is an important factor to take into account since it affects both the rate of functional decline

and the amount of time that renal function is reduced. The terms acute kidney injury (AKI) and chronic kidney disease (CKD) are more recent alternatives to the ancient terms acute renal failure (ARF) and chronic renal failure (CRF) [4].

Diagnosis and characterisation of kidney illnesses that aren't tumor-related are the main goals of renal pathology. To differentiate between renal disease and nephrotoxicity, the kidney damage does not always have to be brought on by chemicals. Furthermore, extrinsic events including diabetes, hypertension, obesity, sepsis, liver failure, and pathological events like sepsis can cause kidney damage brought on by pathological events. There are some similarities between nephrotoxicity and renal pathology despite the definitional variances. The first of these is those both requires alterations in the physical makeup of the nephron, the kidney's functional unit, and are predominantly brought on by renal cell death. This includes alterations to the interstitium, intrarenal blood arteries, glomeruli, tubules, and glomerules. A typical kidney has about a million nephrons, which cooperate to carry out its main tasks, which include filtering waste from the blood, maintaining the body's overall fluid balance, maintaining blood pH, and hormonal functions that support the formation of red blood cells, bone health, and blood pressure regulation. Any of these roles can be changed if enough cells are lost along any region of the nephron. This is especially true of the proximal tubules, which the great majority of nephrotoxins target as their main organ of attack. There are strong similarities between the processes governing renal cell death brought on by nephrotoxins and renal diseases. For instance, ATP depletion, oxidative stress, proximal tubule cell death and loss of the brush border membrane, and cell polarity all contribute to ischemia-induced AKI. In contrast, AKI brought on by the well-known nephrotoxicant cisplatin, cancer chemotherapy, also results in oxidative stress, proximal tubule cell death, and loss of the brush border membrane and polarity. Increased oxidative stress, ATP loss, and proximal tubule cell death are also frequently observed in contrast media-induced nephrotoxicity, which is similarly known to alter renal blood flow and glomerular function. This resembles the symptoms of

diabetic-induced nephropathy. Key events in renal failure brought on by hypertension and hyperglycemia include proteinuria, glomerular fibrosis, and interstitial fibrosis. These events have certain characteristics with glomerular changes brought on by D-penicillamine, furosemide, and gold. Whether the injury is brought on by a nephrotoxicant or a renal disease, kidney damage is classified and staged in the same way. Even if it is now unfeasible to do a thorough analysis of renal pathology, anybody researching nephrotoxicity has to be aware of a number of terminologies and concepts [5].

Mechanism of Nephrotoxicity

Nephrotoxicity can occur due to a variety of causes, such as renal tubular toxicity, inflammation, glomerular destruction, crystal nephropathy, and thrombotic microangiopathy. The kidney typically maintains a steady glomerular filtration rate (GFR) by controlling the pressure in the afferent and efferent arterioles, which is regulated by renal prostaglandin and angiotensin II. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory medicines (NSAIDs) are examples of prostaglandin antagonists that cause glomerular dysfunction. Due to tubular reabsorption and delayed concentration processes, medicines come into touch with the renal proximal renal tubular cells. Through the creation of oxidative stress, which results in tubular mitochondrial damage, toxic substances and medications have the ability to harm the tubular transport system. Amphotericin B, aminoglycosides, and antivirals like adefovir and foscarnet can all harm the tubules [6].

The biochemical and molecular processes of nephrotoxicity has been the subject of several investigations. We now have more knowledge than ever regarding the processes by which nephrotoxicants trigger renal cell death thanks to these research and bioinformatics-based methods. These findings contributed to the development of the idea of “in-common mechanisms,” which are related to DAMPs (damage associated molecular patterns). The fundamental tenet is that nephrotoxicants, notwithstanding their structural diversity, will produce comparable modes of action. The systems eventually open up paths specific to the damaged cell. Although DAMPs are not particular to the kidney, combining

them with established and newly developed biomarkers of renal function will be crucial for overcoming some of the field’s most pressing issues. The processes of cell death caused by nephrotoxicants have drawn a lot of attention. Renal cells undergo all 3 primary kinds of cell death, including apoptosis, autophagy, and necrosis [7]. The mechanisms of apoptosis include intrinsic and extrinsic routes, and it is known that a number of cancer treatments, antibiotics, fungus, mould, metals like mercury, and oxidants can cause the death of renal cells. In the kidney, autophagy has not gotten as much attention as apoptosis. The research that are available demonstrate that a number of cancer treatments, antibiotics, fungi, and moulds trigger autophagy. Numerous research support the idea that autophagy may preserve the kidneys. To find the answer to this issue and the crucial signalling processes that determine whether autophagy is nephrotoxic or nephroprotective, more research is required. Research on autophagy in the kidney is intriguing because its signalling pathways might offer novel targets for treatment of AKI. Numerous substances are known to cause renal necrosis. Many of these substances can also trigger autophagy or apoptosis. All toxicants have a specific mechanism that depends on the cell type, dosage, and duration of exposure. A recent revival in the study of necrosis has given rise to the research of programmed or controlled necrosis. Numerous mechanisms, including those involving the activation of certain caspases, a process typically linked to apoptosis, are involved in programmed necrosis. Other routes involved in programmed necrosis include those mediated by receptors and kinases, such as the mixed lineage kinase and receptor interacting protein kinase pathways. The development of the inflammasome is also included in this. While programmed necrosis has been extensively researched in other organ systems, the kidney has gotten far less attention. As a result, there are numerous options for investigation [8].

Numerous research on nephrotoxicants concentrate on a specific substance or cell. Although such experiments are crucial to comprehend the mechanism of action, it’s possible that they don’t accurately reflect the *in vivo* situation where injury to one part of the nephron affects the other parts of the nephron. Further, patients with AKI or

CKD are seldom exposed to nephrotoxics without one or more mitigating factors, such as hypertension, obesity, liver, lung, or cardiac issues, or the presence of other chemicals like alcohol or cigarette smoke. This is due to the complexity of AKI and CKD. Therefore, additional research is required to evaluate the effects of combinations and comorbidities. Further research is required to determine how age and gender affect the processes of nephrotoxicant-induced cell death. This latter aspect is crucial since children and the elderly make up a sizable portion of patients who develop AKI or CKD [9].

Therefore, the pathogenic mechanisms of drug-induced nephrotoxicity are summarized into the followings:

Alterations of renal intraglomerular hemodynamic

An average intraglomerular pressure of 120 mL per minute, which is influenced by the pressure differences at the afferent and efferent arterioles, maintains adequate glomerular filtration. Prostaglandins in the bloodstream influence afferent arterioles pressure, whereas angiotensin II in the bloodstream influences efferent arterioles and intraglomerular pressure. As a result, NSAIDs like diclofenac, ARBs like valsartan, and ACEIs like captopril severely worsen intraglomerular pressure and lower GFR. Additionally, afferent arteriole vasoconstrictions caused by tacrolimus and cyclosporine are dose-dependent [10].

Renal tubular cytotoxicity

Drugs and their metabolites are among the waste products that are removed from the body by the renal proximal tubules. Proximal tubule cells are particularly vulnerable to drug-induced toxicity and consequent acute kidney damage due to their active secretion and reabsorption processes and ability for biotransformation. Additionally, the proximal tubule epithelium consistently expresses a wide variety of functional transporters and metabolic enzymes that collaborate to facilitate renal drug clearance. Because renal drug transporters are so tightly packed, proximal renal tubules are more sensitive to hazardous substances such as antiretroviral medications and cisplatin [11].

Glomerulonephritis and interstitial nephritis

The inflammation of the glomeruli known as glomerulonephritis is brought on by a variety of nephrotoxic substances, including as gold, interferon, NSAIDs, lithium, hydralazine, and pamidronate. Interstitial nephritis can be brought on by an allergic reaction to a medicine, as is the case with allopurinol, rifampicin, sulfonamide, lansoprazole, and quinolones. NSAIDs, Chinese herbal medicine, and cyclosporine are among the medications that can lead to chronic interstitial nephritis. It is important to diagnose this problem as soon as possible since it might proceed to end-stage renal disease [12].

Drug-induced crystal nephropathy

Numerous medications resulted in the precipitation of insoluble in urine crystals inside the distal renal tubules, which led to an interstitial response and blockage. Sulfonamides, ampicillin, acyclovir, ciprofloxacin, methotrexate, and triamterene are the medications that cause crystals to form most frequently. Most patients with renal impairment experience crystal nephropathy, which is caused by these medicines precipitating at acidic urine. Moreover, tumour lysis during chemotherapy induction, as in lymphoproliferative disorders, results in considerable uric acid and calcium accumulation, which ultimately results in acute renal failure [13].

Drug-induced thrombotic microangiopathy

As shown in several drugs including ticlopidine, cyclosporine, and quinine, drug-induced microangiopathy is caused by an immunological response to the drug that results in thrombotic thrombocytopenic purpura and platelet activations, which ultimately lead to endothelial cytotoxicity [14].

Drug-induced rhabdomyolysis

Due to their direct toxic effects on myocytes or their propensity to make them more vulnerable to the toxic effects of exercise, certain medications have the potential to harm skeletal muscles. Myocytes lyse as a result of this injury, and intracellular myoglobin and creatine kinase are released. Because of its direct toxicity and tubular blockages, myoglobin causes kidney injury. The effects of several substances, including statins, alcohol, heroin, ketamine, and cocaine, have been found to have rhabdomyolytic effects [15].

Conclusion

Blood urea and serum creatinine are less sensitive than KIM-1, Cys C, and NGAL serum levels in the identification of acute kidney damage during nephrotoxicity. The study of nephrotoxicity is still going strong. It should be highlighted that funding for research concentrating on pathologically generated kidney injury, such as that caused by diabetes or heart disease, is still strong, despite a perceived decline in funding for toxicant-induced kidney injury studies. This field is expected to keep expanding as the opioid crisis and obesity pandemic get worse. As a result, experts in the area may wish to focus more on understanding the mechanisms of harm in the context of comorbid conditions or in the presence of additional substances or combinations rather than just studying the mechanisms of single agents alone. Such investigations should modify pertinent exposure techniques and employ therapeutically and ecologically appropriate doses. These studies should also pay attention to how nephrotoxicity differs depending on age and gender.

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