Nephrotoxicity: A Review on Mechanism, Prevention and Emerging Biomarkers for Drug Induced Nephrotoxicity

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***Abstract*— Nephrotoxicity can cause kidney injury by various types of drugs and chemicals. Drug-induced nephrotoxicity must be identified early and prevented. The aim of this review is to present a summary of the mechanisms of drug-induced nephrotoxicity and identification of new biomarkers. Knowledge regarding nephrotoxicity, including the findings that serum creatinine and blood urea are frequently used indicators of nephrotoxicity. We also examine novel biomarkers with improved sensitivity and specificity, such as proteinuria, kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL), to identify nephrotoxicity. Additionally, we understand the strategies for avoiding drug-induced nephrotoxicity. In addition to offering a comprehensive overview of the current state of knowledge in this field, this review emphasizes the significance of early detection and prevention of drug-induced nephrotoxicity.**

***Index Terms*— Nephrotoxicity, Glomerulonephritis, tubular cell toxicity, crystal nephropathy, thrombotic microangiopathy, Neutrophil gelatinase associated lipocalin (NGAL), Kidney injury molecule-1(KIM-1)**

I. INTRODUCTION

The kidney is an important part of the body, that plays a vital role or functions such as detoxification, excretion of toxin, and drugs as well as maintenance of Homeostasis. [5] Nephrotoxicity, generally knows as renal toxicity occurs when the kidneys are unable to properly excrete harmful substances and chemicals or drugs. [4] It is a common and severe illness that cause tubular harm and rapid loss of renal functions. It is a widespread health issue that leads to death. [1] There are numerous types and some drugs that can have many effects on kidney functions. [2] As a result, kidney is regarded as an important organ that for external toxicants. [6] Long term nephrotoxicity is related to an increased risk of heart disease, chronic kidney disease and death over time, sepsis, nephrotoxins and kidney ischemia-reperfusion are the main cause of nephrotoxicity. [3] Drugs causes approximately 20% of nephrotoxicity however, as the normal life span grows medicine for the elderly raised the risk of nephrotoxicity by us to 66%. [7] The reason behind for such drug induced nephrotoxicity is mainly caused by kidney's excretion of drugs and metabolite which exposes its energy dependent structures to excessive concentrations of foreign chemical. [8,9] Nephrotoxicant-induced renal cell death and renal diseases are mediated by very comparable pathways. For instance, ATP depletion, oxidative stress, proximal tubule cell death, and loss of the brush border membrane and cell polarity are all factors in ischemia-induced AKI.[40]

Drug induced nephrotoxicity is defined as when it causes kidney injury by drugs or chemicals either directly or indirectly. [10] Nephrotoxicity can be detected by changes in renal function such as glomerular filtration rate, BUN, Serum Creatinine or urine output. However, it can cause kidney damage without altering any established clinical markers. [11] A simple blood test can detect nephrotoxicity. Blood tests for nephrotoxicity include measuring BUN, serum creatinine, glomerular filtration rate, and creatinine clearance. [12,13] Nephrotic syndrome and hydro electrolytic diseases (HED), which are linked to glomerular and tubular injury, respectively, can appear as either acute or chronic lower glomerular filtration rate (GFR). [14] Therefore, discovery and development of biomarkers that can detect kidney dysfunction at the early stage are needed. The article will explore the pathophysiology of renal toxicity, mechanism of drug induced nephrotoxicity, emerging biomarkers in nephrotoxicity research, and their prevention. It will also touch on related conditions such as glomerulonephritis, offering a comprehensive view of kidney health and toxicity.

II. PATHOPHYSIOLOGY OF NEPHROTOXICITY

2.1 Oxidative stress and Reactive Oxygen Species

Certain medications might cause nephrotoxicity by producing reactive oxygen species (ROS). Because ROS have an unpaired electron, they can attach themselves irreversibly to membranes, organelles, and other macromolecules to harm cells. The hydroxyl radical, hydrogen peroxide, and the superoxide anion are a few examples. Cisplatin, for example, has been shown to induce ROS in the kidney via three mechanisms.[33] Cisplatin depletes glutathione and other antioxidants, altering cellular redox state and increasing endogenous ROS and oxidative stress. Cisplatin may cause mitochondrial dysfunction, leading to increased ROS generation through an inefficient respiratory chain. Finally, Cisplatin may cause ROS production via the cytochrome P450 system. ROS can disrupt cell function and even cause cell death through various signalling pathways.[34]

2.2 Apoptosis

Pro-apoptotic bcl-2 family proteins Bax and Bak generate pores in mitochondria's outer membrane during the intrinsic pathway. Cytochrome C and other apoptogenic components are released as a result of MOMP. Cytochrome c interacts to Apaf-1 in the cytosol, causing conformational changes that attract and activate caspase-9. Caspase 9 activates executioner caspases, resulting in apoptosis. Bcl-2 proteins, including bcl-xL and bcl-2, bind to Bax and Bak and inhibit MOMP in healthy cells. Both intrinsic and death receptor-mediated pathways of caspase – mediated cell death are exhibited by Rodent models of nephrotoxicity. Bax-deficient mice did not have renal damage from cisplatin, and their proximal tubular cells were resistant to apoptosis. In terms of the extrinsic route, animals with cisplatin-induced renal dysfunction and structural damage were lessened by tumor necrosis factor (TNF)-a deletion and TNF-a inhibitors.[31] Furthermore, animals exposed to cisplatin and colistin showed increased production of death-receptor ligands (TNF-a and Fas ligand) as well as caspase-8 activation. Crucially, caspase-8 activation can cause renal cells to undergo intrinsic apoptosis.[32]

2.3 DAMPs and Inflammasome

Necrotic cells leak unprocessed internal contents that cause DAMPs when their plasma membrane ruptures. DAMPs cause innate immunological, endothelial, and epithelial cells' membrane-bound or cytosolic pattern recognition receptors to become active. By encouraging the release of pro-inflammatory mediators and attracting immune cells to enter the tissue, this triggers an immunological response. Crucially, this also starts pyroptosis, an inflammatory type of cell death.[35]

III. MECHANISM OF DRUG INDUCED NEPHROTOXICITY

Nephrotoxicity can be caused by a variety of mechanisms, such as glomerular injury, inflammation, renal tubular toxicity, crystal nephropathy, and thrombotic microangiopathy. Tubular reabsorption and extended concentration processes, medicines come into touch with renal proximal renal tubular cells. Drugs and toxic substances have the ability to harm the tubular transport system by causing oxidative stress, which damages the tubular mitochondria.

Antivirals such adefovir and foscarnet, aminoglycosides, and amphotericin B are the medications that harm tubules. [15]

3.1 Alterations of renal intraglomerular hemodynamic

The glomerular filtration rate (GFR) for young, healthy individuals is 120 millilitres per minute. By controlling blood flow in afferent and efferent arteries for intraglomerular pressure adjustments or maintenance, kidneys can maintain a steady filtration rate and the displacement of urine. The enlargement of afferent arteries is promoted by prostaglandin circulation. It has been demonstrated that Anti-prostaglandin medications with anti-angiotensin activity, such as angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors, or nonsteroidal anti-inflammatory medicines (NSAIDs), cause glomerular nephrotoxicity. [16,17]

3.2 Inflammation

Nephrotoxic drugs often induce inflammation in glomerulus, proximal tubules, and surrounding cellular matrix, and then enhance the kidney tissue. Inflammation that disturbs normal kidney functions and induce toxicity includes glomerulonephritis, acute and chronic interstitial nephritis. It has been demonstrated that proteinuria and glomerulonephritis are closely connected. NSAIDs and antibacterial medications like rifampicin can cause acute interstitial nephritis, a form of drug-induced immune response. Long term use of analgesic, lithium, calcineurin inhibitors, and certain anticancer medications can cause Chronic interstitial nephritis [18,19]

3.3 Tubular cell toxicity

Drug toxicity has a significant impact on the renal tubules, particularly the proximal tubule cells, during concentration and absorption through the glomerulus.

The tubules' damaged mitochondria, the tubular transport system's disruption, and increase in oxidative stress by the production of free radicals that can cause cytotoxicity. [20]

3.4 Drug-induced crystal nephropathy

Drugs can form insoluble crystals in urine, producing interstitial reactions and blockage in the distal renal tubules. Crystals are commonly produced by medications such as sulphonamides, ampicillin, acyclovir, ciprofloxacin, methotrexate, and triamterene. These drugs precipitate in acidic urine, leading to crystal nephropathy in patients with renal impairment. [21]

3.5 Drug-induced thrombotic microangiopathy

A drug-induced immunological response causes thrombotic thrombocytopenic purpura and platelet activations, which ultimately result in endothelial cytotoxicity and drug-induced microangiopathy. [22]

IV. EMERGING BIOMARKERS IN NEPHROTOXICITY

Blood urea and serum creatinine are the usual indicators of nephrotoxicity and renal dysfunction; they are specific but have low sensitivity for identifying early renal disorder. Therefore, novel biomarkers that are more sensitive and highly specific and provide information about the location of underlying renal damage were needed to detect the initial renal injury. [23]

4.1 Urinary proteins with enzymatic activity

As nephrotoxic biomarkers, the enzymes found in tubular epithelial cells leak into the urine in cases of acute or chronic kidney damage brought on by exposure to nephrotoxic substances, diabetic kidney disease, hypertension, renal ischemia, transplantation, or glomerular diseases. N-acetyl-D-glucosaminidase, α-glutathione-S-transferase, γ-glutamyl transpeptidase, π-glutathione-S-transferase, alanine aminopeptidase, and alkaline phosphatase are biomarkers associated with urine proteins exhibiting enzymatic activity. [24]

4.2 Proteinuria

By filtering, the glomerulus normally prevents high molecular weight proteins from migrating from the blood to the nephron lumen. However, in certain clinical conditions, selective penetration through the glomerulus is impaired, resulting in the detection of high molecular weight proteins in the urine [25]. Albumin is one of the high molecular weight proteins that can detect kidney injury and is used to diagnose diabetes and altered glomerular filtration early.

4.3 Neutrophil gelatinase-associated lipocalin (NGAL)

A 25 kDa protein called NGAL attaches itself to gelatinase in certain neutrophil granulocytes. It is produced throughout the granulocyte maturation process [26], and it is frequently increased in epithelial cells through cancer or inflammation. NGAL is regarded as a sensitive biomarker for the early diagnosis of acute kidney injury because drug-induced nephrotoxicity or ischemia increases its expression in proximal tubule cells. Infection and infection also cause a rise in the blood's NGAL content.[27]

4.4 Kidney injury molecule-1 (KIM-1)

KIM-1, a type I transmembrane glycoprotein, is one of the gene families that make up T-cell immunoglobulin mucin (Tim). It is recognized to feature a lengthy mucin-like domain in the extracellular area at the top of an immunoglobulin-like domain made up of six odd cysteines. Hepatitis A virus cellular receptor 1 is another name for it [28]. KIM-1 can be employed as a more sensitive biomarker than conventional nephrotoxic indicators like BUN, serum creatinine, and proteinuria when the kidney is damaged by ischemia or reperfusion or exposed to toxic chemicals like cisplatin.

4.5 Cytokines

Polypeptides called cytokines mediate inflammation and immunological responses and control a number of critical biological functions. Repairing injured tissues is tightly linked to a number of cytokines. These include tumor necrosis factor, colony-stimulating factors, interleukins [38], interferons, and numerous growth factors that have demonstrated potential as biomarkers of nephrotoxicity due to their involvement in glomerular and tubular damage.[39]

4.6 Clusterin

The cytoplasm of proximal convoluted tubules or the end of distal convoluted tubules (DCT), including the connecting tubule in the kidney cortex, contain clusterin, a sulfated glycoprotein consisting of 426 amino acids. Because it is found in the urine of individuals with acute renal damage and increases in a variety of kidney illnesses, it can be utilized as a

biomarker. Remarkably, glomerulonephritis is exacerbated by clusterin deficiency [37].

4.7 Type IV collagen

A major part of the basement membrane, type IV collagen, is found in higher concentrations in the urine after glomerulus injury. Since it is too big to fit through the glomerulus' outer membrane, its presence in the urine serves as a sensitive marker for glomerular alterations in the extracellular matrix's structure and is therefore a crucial biomarker of nephrotoxicity [36].

V. RISK FACTOR RELATED TO DRUG INDUCED NEPHROTOXICITY

5.1 Patient factors

Patients over 60 with diabetes mellitus, underlying chronic renal insufficiency, dehydration, and concomitant heart failure are at an increased risk of developing acute kidney injury. The nephrotoxic effects of hormonal changes are more likely to affect males than females, hence hereditary and gender differences are common contributing factors to the risk of drug-induced nephrotoxicity. Hepatic insufficiency, heart failure, and dehydration are among conditions that increase the risk of drug-induced renal impairment. [29]

5.2 Drug factors

Some medications, such aminoglycosides and cyclosporine, have the potential to be nephrotoxic by nature. long-term use of certain medications, like as allopurinol, can cause 98 crystal nephropathy and chronic interstitial nephritis. Additionally, the risk of kidney impairment is increased when nephrotoxic medications, such as diuretics and aminoglycosides, are combined. [30]

VI. PREVENTION MEASURES

1.Using medications that are effective but not nephrotoxic.
2. Determining and reducing the underlying risk factors.
3. Evaluation of baseline renal function prior to starting treatment.
4. Dietary adjustments based on renal function.
5. Before beginning treatment, a GFR evaluation is required for high-risk individuals.
6.Adhering to the Food and Drug Administration's guidelines when using medications.
7. Treating underlying acute and chronic illnesses and drinking enough water.
8. Effective communication between the room pharmacist and the knowledgeable doctor regarding medication dosage monitoring and dose-response curve analysis. [41-43]

VII. CONCLUSION

By understanding the kidney health and disease, the great impact of the biomarkers and renal toxicity are explored. The early detection capabilities of the biomarkers like urinary proteins such as KIM-1 and NGAL to proteinuria and other biomarkers insights into the mechanisms of nephrotoxicity. This progress has an effect on drug development, clinical trials, and early diagnosis approach, that leads to improve patient health and reduce the toxicity or other kidney disease. The field of nephrotoxicity research continues to develop, get new opportunities to detect, monitor, and prevent kidney harm. As we search deeper into the complexities of renal toxicity, the combination of these biomarkers with traditional clinical biomarkers has the possibilities to modernize nephrology practice. Nephrotoxicity or the kidney related condition like glomerulonephritis are decreased by the advancement in effective ways of the biomarkers and enhanced the quality of life for patient at high risk of toxicity.

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