Nephrotoxicity, its mechanism and biomarkers: A systematic review

Hemalatha S[1*], Shivakumar Swamy[2], Narayan Sha Sonar[3], Hariprasad M.G[4], Nandini S[5]

[1,3,5]Student, [2]Principle and Professor, [4]Professor, Dept. of Pharmacology, Mallige College Of Pharmacy, Bengaluru, Karnataka, India

***Corresponding Author: Hemalatha S**
Email: lathahema3396@gmail.com

Abstract
Nephrotoxicity is a common condition responsible for variety of pathologic conditions on kidney due to the destruction of renal function by one or more nephrotic substance. For renal injury to occur, combination of risk factors (drug, kidney and patient related factors) are generally present. The mechanism involved in nephrotoxicity include altered intraglomerular haemodynamic, crystal nephropathy, inflammation, tubular cell necrosis, throbotic microangiopathy, rabdomyolysis. Nephrotoxicity can be assessed by estimating the blood urea nitrogen (BUN), centralization of serum creatinine, glomerular filtration rate and creatinine clearance. Development of new biomarkers are required for specific diagnosis of nephrotoxicity at earlier stages.

Keywords: Nephrotoxicity, Risk factors, Mechanism, Biomarkers.

Introduction
Kidney assumes a significant role in filtration of some noxious substances, which are the fundamental driver for the nephrotoxicity.[1] Medication instigated nephrotoxicity is a very basic condition and is answerable for an assortment of obsessive impacts on the kidneys[2]. The nephrotoxicity of medications is a convoluted procedure that includes a blend of elements. These incorporate the natural nephrotoxic capability of medication, basic patient attributes that improve their hazard for kidney damage, and the digestion and discharge of the potential culpable specialist by the kidney.[3] Acute renal failure (ARF) represented 20% of all ARF case.[2] Finlay et al. characterize nephrotoxic medications (ND) as therapeutic operators that can possibly cause unfriendly impacts on renal capacity because of direct harmfulness or traded off renal perfusion, and this lethality may rely upon the clinical setting included. The sorts of kidney brokenness that are induced by nephrotoxic medications incorporate acute tubular necrosis, glomerular and tubulointerstitial damage, haemodynamically interceded damage and obstructive nephropathy.[4] Exposure to drugs regularly brings about lethality in kidney which speaks to the significant control framework keeping up homeostasis of body and along these lines is particularly powerless to xenobiotics.[5]

Most medications found to cause nephrotoxicity apply harmful impacts by one or more pathogenic components. These incorporate adjusted intraglomerular hemodynamics, tubular cell lethality, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy[6]. Nephrotoxicity can be analyzed through a basic blood test. Assessment of nephrotoxicity through blood tests incorporates the estimations of blood urea nitrogen (BUN), centralization of serum creatinine, glomerular filtration rate and creatinine clearance.[5] There is an ascent in the advancement of biomarkers for recognizing nephrotoxicity, as standard strategies are not dependable because of absence of particularity and sensitivity.[1] However, these evaluations of nephrotoxicity are just conceivable when a larger part of kidney work is damaged.[5]

In this article we summarize the risk factors (hazard factors), mechanism of nephrotoxicity and biomarkers of nephrotoxicity.

Hazard factors[3]
Renal explicit components

1. High rate of blood conveyance to kidney [approximately 20% of heart output].

2. Increase in convergence of medication in interstitium and renal medulla.
3. Formation of Reactive Oxygen Species(ROS) and nephrotoxic endless supply of medication.
4. High metabolic rate of tubular cell [loop of henle].
5. Uptake of medications by proximal tubule.

Patient related elements

1. Old age >65 years
2. Nephrotic disorder
3. Cirrhosis
4. Kidney hyperfusion
5. Acute kidney disease/Chronic kidney disease
6. Metabolic perturbation
7. Increased unfavorably susceptible medication reaction because of resistant reaction qualitiesz
8. Pharmacogenetics favoring drug poisonous quality

Medication related elements

1. Prolongation of dosing times of medications and its exposure.
2. Potent direct nephrotoxic impact of medications.
3. Enhanced nephrotoxicity because of blend of medications.
4. Competition among endogenous and exogenous poisons for transporter, increment poisonous gathering inside tubular cell.
5. Insoluble metabolite with intratubular crystal precipitation.

Mechanism of nephrotoxicity

The mechanism intervening renal cell death incited by nephrotoxicants and renal pathologies are strikingly comparable. For instance, ischemia-instigated Acute kidney injury includes ATP consumption, oxidative stress, proximal tubule cell passing and loss of the brush fringe film, and cell extremity[7]. General systems that reason nephrotoxicity remember changes for glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy[8].

Changes in intraglomerular hemodynamics

In a generally solid youthful grown-up, around 120 mL of plasma is adjusted under strain through the glomerulus every moment, which relates to the glomerular filtration rate (GFR). The kidney keeps up or autoregulates intraglomerular pressure by balancing the afferent and efferent blood vessel tone to safeguard GFR and urine yield. For example, in patients with volume exhaustion, renal per-combination relies upon circling prostaglandins to vasodilate the afferent arterioles, permitting more blood course through the glomerulus.

Simultaneously, intraglomerular pressure is continued by the activity of angiotensin-II–intervened vasoconstriction of the efferent arteriole. Medications with antiprostaglandin movement (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) or those with antiangiotensin-II-action (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]) can meddle with the kidneys' capacity to autoregulate glomerular weight and decreasing GFR. Other medications, for example, calcineurin-inhibitors (e.g., cyclosporine (46 mator], tacrolimus [Prograf]), cause portion subordinate vasoconstriction of the afferent arterioles, prompting renal hindrance in danger patients.[9]

Tubular cell lethality

Since renal tubules, particularly proximal tubule cells, are presented to drugs during the time spent fixation and reabsorption through the glomerulus, they are affected incredibly by tranquilize harmfulness.[10] Cytotoxicity happens due to the damaged mitochondria in tubules, the upset tubular transport system, and the expansion in oxidative stress by free radicles. The cytotoxicity inciting drugs incorporate aminoglycoside antibiotics, antifungal operators, for example, amphotericin B, hostile to retroviral medications, for example, adefovir, anticancer medications (cisplatin and foscarnet).[11]

Inflammation

Nephrotoxic medications frequently actuate inflammation in glomerulus, proximal tubules, and encompassing cell matrix, and afterward fiberize the kidney tissue. Inflammation that upsets typical kidney works and incites harmfulness incorporates glomerulonephritis, intense and incessant interstitial nephritis. Glomerulonephritis has been demonstrated to be firmly identified with proteinuria.[10] Acute

interstitial nephritis, a kind of medication initiated insusceptible reaction, is instigated by NSAIDs and anti-biotic medications, for example, rifampicin. Chronic interstitial nephritis happens habitually by long haul utilization of calcineurin inhibitors, lithium, some anticancer medications or analgesics.[12]

Crystal nephropathy

Renal disability may result from the utilization of medications that produce crystal that are insoluble in human urine. The crystals hasten, for the most part inside the distal tubular lumen, discouraging urine stream and inspiring an interstitial reaction. Commonly prescribed drugs related with generation of crystals incorporate antibiotics (e.g., ampicillin, ciprofloxacin [Cipro], sulfonamides); antivirals (e.g., acyclovir, foscarnet, ganciclovir [Cytovene]); indinavir; methotrexate; and triamterene (Dyrenium). The probability of crystal precipitation relies upon the convergence of the medication in the urine and the urinary pH. Patients most in danger of crystal nephropathy are those with volume consumption and fundamental renal insufficiency.[13]

Rhabdomyolysis

Rhabdomyolysis is a condition wherein muscle fiber contents are discharged into the circulation system when skeletal muscle is decimated because of some damage. As renal muscle cells disincorporate because of damage in muscle tissue, myoglobin and serum creatine kinase are discharged into the blood. Discharged myoglobin debases and discourages the capacity of filtration in kidney coming about acute tubular necrosis or renal failure.[8] Significant reasons for rhabdomyolysis are medicate maltreatment from heroin, methadone, methamphetamine, and statin just as liquor abuse[5,14]

Thrombotic microangiopathy:

In thrombotic microangiopathy, organ damage is brought about by platelet thrombi in the microcirculation, as in thrombotic thrombocytopenic purpura. Mechanisms of renal damage auxiliary to tranquilize incited thrombotic microangiopathy incorporate an insusceptible interceded response or direct endothelial toxicity. Drugs regularly connected with this pathogenic system of nephrotoxicity incorporate antiplatelet drugs (e.g., clopidogrel [Plavix], ticlopidine [ticlid]), cyclosporine, mitomycin-C (Mutamycin), and quinine (Qualaquin).[15]

Biomarkers for nephrotoxicity:

Numerous pathophysiologic components referenced above are legitimately identified with the acceptance of nephrotoxicity. Since conventional standard markers, for example, BUN and serum creatinine have low affectability and explicitness, the planning of the finding and treatment are regularly postponed. Along these lines, improvement of new biomarkers is required for the particular analysis of nephrotoxicity at prior stages.[16]

Biomarkers assign the biomolecules indicating the connection between exogenous dangerous substances and illnesses. For the most part, biomarkers empower us to decide early damage to wellbeing brought about by presentation to exogenous lethal substances, and give an understanding into the system of the beginning of these toxicants to antagonistically influence certain gatherings or people. The recognizable proof of biomarkers that can be resolved from blood or urine came about because of presentation to a nephrotoxicant is a promising methodology. Particularly, urine is viewed as appealing and effective example since it is non-obtrusive and simple to be gotten in significant amounts.

Biomarker competitors have been distinguished for the appraisal of nephrotoxicity. Albeit some of them neglect to give particularity and affectability of biomarkers, a few promising competitors have been demonstrated for analysis of nephrotoxicity.[5,16]

Urinary proteins with enzymatic action

In the event that there is acute or chronic kidney damage because of presentation to nephrotoxic substances, diabetic kidney sickness, hyper-pressure, renal ischemia, transplant, or glomerular illnesses, the compounds present in rounded epithelial cells are spilled into the urine and can be identified as nephrotoxic biomarkers. Biomarkers related with urinary proteins with enzymatic movement include alanine aminopeptidase, antacid phosphatase, α-glutathione-S-transferase, γ-glutamyl transpeptidase,

π-glutathione-S-transferase, and N-acetyl-D-glucosaminidase.[16]

Kidney injury molecule1 (KIM-1)

KIM-1 is a sort I transmembrane glycoprotein and one of the quality families that structure T-cell immunoglobulin mucin (Tim) and is known to have an immunoglobulin-like domain comprising of six strange cysteine and fixing a long mucin-like space in extracellular locale. It is otherwise called hepatitis. A virus cell receptor 1.[17] At the point when the kidney is presented to toxic substances, for example, cisplatin or gets harmed by ischemia or reperfusion, KIM-1 can be utilized as a more touchy biomarker than customary nephrotoxic biomarkers, for example, BUN, serum creatinine, and proteinuria KIM-1 articulation has been accounted for to associate with proximal tubular damage, renal tubular regeneration and invulnerable reaction by nephrotoxicants. The mRNA and protein levels of KIM-1 are exceptionally communicated in harmed kidney. KIM-1 is ex-presented toward the tubular lumen and extracellular domain (or ectodomain) of KIM-1 is cut by matrix metalloproteinase and afterward at long last discharged in urine KIM-1 up-guideline shows up quickly and is effectively identified in the urine upon nephrotoxicity. Since extracellular domain of KIM-1 is truly steady and simple to be distinguished. KIM-1 has been considered as a non-intrusive as a non-obtrusive biomarker for human renal proximal tubular damage.[5]

Proteinuria

In ordinary conditions, the glomerulus limits the relocation of high molecular weight proteins from blood to nephron lumen by filtration. In some pathological states, however, high molecular weight proteins can be detected in the urine in light of the fact that the specific infiltration through glomerulus isn't working appropriately. High molecular weight proteins that can reveal kidney damage incorporate albumin which can be utilized for early conclusion of changed glomerular filtration and diabetes, transferrin which transports iron and speaks to glomerular damage all the more delicately, and immunoglobulin G that shows basic damage in the glomerulus[5].

Low molecular weight proteins created in different organs are filtered and reabsorbed in the glomerulus and not discharged from the proximal tubule. An expansion of the separated low molecular weight proteins speaks to that assimilation in the glomerulus and proximal tubule isn't sufficient, which implies there might be cell damage or over-burden.[11] In this manner, kidney damage by harmfulness can be distinguished before utilizing estimations of proteins in urine. Low molecular weight proteins that speak to tubular damage are β2-microglobuluin α1-microglobulin, retinol-restricting protein which transports retinol from liver to different organs , and cystatin-C, an inhibitor of cysteine proteinase.[18]

Clusterin

Clusterin, a sulfated glycoprotein with 426 amino acids, is available in the cytoplasm of proximal convoluted tubule or toward the finish of distal convoluted tubule (DCT) incorporating interfacing tubule in the kidney cortex. It tends to be utilized as a biomarker because it increments in different kidney disease and is identified in the urine of patients with acute kidney damage. Curiously, the exhaustion of clusterin declines glomerulonephritis.[5]

Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is a 25kDa protein that ties to gelatinase specifically neutrophil granulocytes. It is synthesized in the development procedure of granulocytes, and regularly actuated in epithelial cells by inflammation or tumorigenesis[19]. Since NGAL articulation is expanded in proximal tubule cells by sedate incited nephrotoxicity or ischemia, it is known as a delicate biomarker for the early finding of acute kidney damage. The grouping of NGAL in blood additionally increments in infection and inflammation.[5]

Cytokines

Cytokines are polypeptides that direct numerous significant biological procedures and act as arbiters of inflammation and immune reactions. Numerous cytokines are intently connected with the fix of damaged tissues. Among them, interferons, interleukins , tumor necrosis factor, colony stimulating factor, and several growth factors indicated potential

as biomarkers of nephrotoxicity since they are associated with glomerular and tubular damage and fix.[5]

Type IV collagen

Type IV collagen, a fundamental part of the cellar layer, increments in the urine following damage of the glomerulus. Because it is too enormous to even think about passing through the external layer of the glomerulus, its fixation in the urine is a touchy pointer for glomerular changes in the structure of the extracellular matrix and in this way a significant biomarker of nephrotoxicity.[5,20]

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Conflict of Interest

None.

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