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A REVIW ON DRUG INDUCED NEPHROTOXICITY

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ABSTRACT :

Nephrotoxicity is the result of impaired kidney function brought on by endogenous or exogenous toxicants, impairing kidney-specific excretion and detoxification processes.[1] It is a common side effect of many widely used drugs nowadays. Acute renal failure, chronic interstitial nephritis, and the nephrotic syndrome are the three clinical syndromes that can be identified in drug-induced nephropathy.[2] The kidney is another important target for drug- induced toxic effects, in addition to the liver. Since the kidneys are one of the primary organs of excretion, they naturally absorb a larger percentage of circulating medications and substances. They also get roughly 25% of cardiac output. Many substances, including heavy metals, chemicals, fungus toxins, and a wide range of medications, have been linked to renal toxicity.[3] One of the main causative causes of end-stage renal disease (ESRD), acute renal failure (ARF), chronic kidney disease (CKD), and acute kidney injury (AKI) is drug-induced nephrotoxicity.[4] Changes in glomerular hemodynamic, tubular cell toxicity, infiltration, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy are among the mechanisms for drug-induced nephrotoxicity. Nephrotoxicity has been evaluated by the identification of biomarkers. To effectively prevent drug-induced nephrotoxicity, new biomarkers that can diagnose kidney damage early and more precisely must be discovered and developed.[1]

MECHANISM OF DRUG-INDUCED NEPHROTOXICITY :

Drug excretion begins with blood filtration by the glomerulus in the nephrons, where waste metabolites and unbound medicines are eliminated to the primary urine while drugs bound to proteins remain in the bloodstream. After entering the tubules, the primary urine undergoes proximal tubule reabsorption of significant components. In the meanwhile, materials such as ions and other kinds of wastes can be eliminated even more by means of active tubular secretion.[6] Kidney damage may develop during these processes in the renal vascular supply, glomerulus, tubule interstitium, and collecting ducts, among other renal components. Damage to these kidney sections is typically brought on by one or more of the following mechanisms: inflammation, rhabdomyolysis, tubular cell toxicity, altered glomerular hemodynamic, thrombotic microangiopathy and crystal nephropathy. [7,8]

CHANGES IN GLOMERULAR HEMODYNAMICS :

The glomerular filtration rate (GFR) for young, healthy individuals is 120 millilitres per minute. By controlling blood flow in the afferent and efferent arteries to maintain or modify intraglomerular pressure, kidneys can maintain a steady filtration rate and urine displacement. Afferent artery enlargement is accomplished via prostaglandin circulation.[9] Nephrotoxicity in the glomerulus has been demonstrated to be caused by anti-prostaglandin medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or medications with anti-angiotensin activity to prevent blood pressure elevation, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).[10]

TUBULAR CELL TOXICITY :

Drug toxicity has a significant impact on renal tubules, particularly proximal tubule cells, since they are exposed to medicines during the process of concentration and reabsorption through the glomerulus.[11] Damage to the mitochondria in tubules, disruption of the tubular transport system, and an increase in oxidative stress brought on by the production of free radicals are the causes of cytotoxicity.[8,11] Antibiotics with aminoglycosides, antifungal medications like amphotericin B, anti-retroviral medications like adefovir, and anticancer medications like cisplatin and foscarnet are among the medications that cause cytotoxicity.[11,12,13]

INFLAMMATION :

Nephrotoxic medicines fiberize the kidney tissue by inducing inflammation in the glomerulus, proximal tubules, and surrounding cellular matrix. Acute and chronic interstitial nephritis, glomerulonephritis, and other forms of inflammation can cause toxicity and interfere with normal kidney functions. Proteinuria and glomerulonephritis have been demonstrated to be tightly associated.[11]NSAIDs and antibiotics like rifampicin can cause acute interstitial nephritis, a type of drug-induced immune response.[13] Long-term use of calcineurin inhibitors, lithium, some anticancer drugs, or analgesics can cause chronic interstitial nephritis. In the case of chronic interstitial nephritis, early detection is particularly important because it is difficult to diagnose until most of the kidney's functionality is destroyed.[1]

CRYSTAL NEPHROPATHY :

Medication that causes insoluble crystals in human urine can also cause disorders in renal function.[14] The concentration of the drug and the pH of the urine both affect the production of insoluble crystals. Medication that can cause crystal nephropathy includes antiviral medications like acyclovir and antibiotics like ampicillin.[11,12]

RHABDOMYOLYSIS :

When skeletal muscle is damaged owing to an accident, a condition known as rhabdomyolysis occurs where the contents of the muscle fibres are released into the bloodstream. Serum creatine kinase and myoglobin are released into the bloodstream when kidney muscle cells break down as a result of injury to the muscle. Myoglobin released into the bloodstream weakens and inhibits the kidney's ability to filter substances, leading to acute tubular necrosis or renal failure.[15] Heroin, methadone, methamphetamine, statins, and alcoholism are the main causes of rhabdomyolysis.[15,16]

THROMBOTIC MICROANGIOPATHY :

Drug-induced thrombotic microangiopathy is caused by direct toxicity to renal epithelial cells or inflammation that damages organs.[17] It has been demonstrated that antiplatelet medications such as quinine, mitomycin-C, and cyclosporin can result in thrombotic microangiopathy.[17,18]

CLINICAL IMPACT :

1. DRUG INDUCED ACUTE RENAL FAILURE

ARF, which is characterised by a rise in serum creatinine of at least 0.5 mg/dL over the course of 24 hours, can be brought on by a variety of drugs through several pathways. Prerenal type ARF is associated with medications that produce vasoconstriction or intravascular volume depletion. Prerenal azotaemia and volume depletion can result from the use of diuretics alone or in combination. Volume depletion or ineffective arterial blood volume may be caused by elevated levels of renal vasoregulatory substances, such as elevated serum angiotensin or vasodilator prostaglandins, to maintain maximum filtration. These conditions include congestive heart failure, cirrhosis, nephrosis, and patients with underlying compromised renal function. In these circumstances, the administration of pharmaceuticals such nonsteroidal anti- inflammatory drugs (NSAIDs) or angiotensin converting enzyme (ACE) inhibitors inhibits nephronal autoregulation, leading to ARF. More recently, the immunosuppressive medication cyclosporin has been linked to functional renal insufficiency. Afferent arteriole vasoconstriction is brought on by cyclosporin; the sympathetic nervous system may play a role in mediating this effect. The impact is reversible upon stopping the medication and is somewhat offset by an increase in renal prostaglandin synthesis. When cyclosporin is taken with an NSAID or an ACE inhibitor, there is a potential for an elevated risk of acute renal failure.[5]

2. ACUTE TUBULAR NECROSIS

The most prevalent type of medication nephrotoxicity is acute tubular necrosis, which is brought on by the drug's direct toxic action on the tubular cells (particularly the proximal tubular cells). Numerous medications have the potential to induce the illness; among them are aminoglycoside antibiotics, amphotericin B, contrast agents, and cyclosporin. Histologically, fluctuating necrosis of the tubular cells, leaving exposed regions of the tubular basement membrane, and indications of regeneration with the creation of new tubules are the characteristics of acute tubular necrosis. Oedema and cellular infiltration are minor interstitial alterations that can occasionally be detected, particularly near the cortico-medullary junction. It might occasionally be challenging to distinguish this illness from acute interstitial nephritis in the latter cases.[2]

- **AMINOGLYCOSIDES**

Antibiotics called aminoglycosides (AMGs), which include gentamicin, tobramycin, amikacin, netilmicin, neomycin, and streptomycin, are commonly used in clinical settings to treat infections caused by both gram-positive and gram-negative bacteria.[19,20] Three primary mechanisms—renal tubular blockage, renal vasoconstriction, and mesangial contraction— allow AMG to have harmful effects on the kidneys. The principal mechanism of AMG-induced nephrotoxicity is tubular cytotoxicity.[19] Gentamicin or other AMG treatment of animals or cultivated tubular epithelial cells causes these cells to undergo necrosis and apoptosis. AMG

agents accumulate in lysosomes, the Golgi apparatus, and the endoplasmic reticulum as a consequence of endocytosis. After crossing the threshold, the AMG build up in the cytosol, interact with the mitochondria, and cause necrosis and apoptosis. AMG inhibits many cell membrane transporters, which impairs tubular reabsorption in addition to tubular cell death. Moreover, AMG causes mesangial constriction and increased intracellular calcium levels. Following AMG treatment, a number of factors are elevated, including platelet-activating factor (PAF), endothelin-1, and thromboxane A2, which are released from endothelial and mesangial cells. These elements increase vasoconstriction and have a paracrine effect on vascular myocytes, which lowers the glomerular filtration rate (GFR). Following AMG treatment, there is a decrease in renal blood flow in addition to tubular cell death and decreased GFR. Clinical signs of nephrotoxicity caused by AMG include proteinuria, glycosuria, hypokalaemia, hypocalcaemia, hypomagnesaemia, non-oliguric ARF, and proximal tubular dysfunction. As with cisplatin, the best ways to reduce toxicity are to use the lowest dose possible, monitor renal function while on therapy, and refrain from taking AMGs in combination with other medications that may be nephrotoxic.[4]

- **AMPHOTERICIN B**

One of the best antifungal medications available is amphotericin B, but its use has been restricted because of its high rate of nephrotoxicity in clinical settings. Amphotericin B therapy, on the one hand, causes tubular injury directly through cell destruction since it can break down fungal cell membranes by

binding ergosterol and rapidly leaking K^+, Na^+, H^+, and Cl^-. The same processes in renal tubular cells may alter the membrane's permeability, which would then lead to tubular dysfunction. However, amphotericin B may also cause vasoconstriction, which lowers GFR and renal blood flow and ultimately results in ischemia injury. A number of lipid formulations of amphotericin B, known as liposomal amphotericin B (LAMB), amphotericin B colloidal dispersion (ABCD), and amphotericin B lipid complex (ABLC), have been created in an effort to lessen toxicity. Since lipid complex formulations ABCD and ABLC have lower serum concentrations than amphotericin B, their nephrotoxicity is diminished. Compared to amphotericin B, the LAMB has less nephrotoxicity, according to three randomised clinical trials.[4]

- **CONTRAST AGENTS**

Contrast agents are frequently employed in medical procedures to improve the contrast of imaging methods. Nephropathy brought on by contrast drugs is the main adverse impact. According to estimates, 11–12% of AKI in hospitals is caused by contrast agents. Serum creatinine levels typically increase 24-48 hours after contrast agent exposure, peak on the second or third day, and then revert to baseline levels in two weeks. Numerous contrast agents produce adenosine from endothelial cells, produce reactive oxygen species, create medullary hypoxia, and activate other mitochondrial pathways to cause renal tubular cytotoxicity. The different kinds of contrast agents that are available are divided into three categories based on their osmolality: iso-osmolar contrast agents (isotonic to plasma), low-osmolar contrast agents (two to three times plasma), and high-osmolar contrast agents (5-8 times plasma). In high-risk patients undergoing arteriography, the impairment of kidney function caused by iso-osmolar
non-ionic iodinated contrast agent iodixanol is significantly smaller than that of low-osmolar non-ionic contrast medium iohexol. The increased stiffness and decreased deformability of erythrocytes caused by the higher osmolality of contrast agents might also hinder their passage through the vasa recta, resulting in a decrease in oxygen. Additionally, the osmotic load typically exacerbates the mismatch between the supply and demand of oxygen by raising the need for oxygen. The viscosity and ionic strength of the contrast agents are linked to nephrotoxicity in addition to the reagent's osmolarity. Contrast drugs have the ability to raise renal tubular viscosity, which raises interstitial pressure and reduces medullary blood perfusion. To lower the danger of contrast agent-induced nephrotoxicity, less toxic contrast agents should be developed and utilised wherever feasible. As a result, alternative imaging techniques without contrast agents should be given priority.[4]

- **CYCLOSPORIN**

One of the most effective immunosuppressive medications for treating autoimmune disorders and preventing organ transplant rejection is cyclosporin. It is a neutral fungal metabolite that is insoluble in water and is delivered in a lipid or organic solvent. It is made up of 11 amino acids that are primarily hydrophobic, one of which is specific to cyclosporin. The hepatic cytochrome P450 system breaks down the medication, which is then eliminated in the bile. Nephrotoxicity is one of the principal adverse effects of cyclosporin. Clinically, patients experience hypertension, oedema, and fluid retention. Serum creatinine levels often gradually rise along with hyperkalaemia and occasionally metabolic acidosis. Upon lowering or stopping the dosage, renal function improves. Histologically, either vascular or tubular alterations mediate cyclosporin's nephrotoxicity. The proximal convoluted tubules' epithelium contains eosinophil inclusions and intracellular vacuoles in the latter case. These modifications, therefore, are not exclusive to cyclosporin. Epithelium necrosis is a frequent occurrence, especially in patients undergoing renal transplants. The average daily dosage is a significant risk factor for the development of renal insufficiency. When cyclosporin was first prescribed, almost all patients had nephrotoxicity at dosages as high as 17.5 mg/kg every day. Much lower cyclosporin dosages (maximum limit around 12 mg/kg daily) are utilised in the majority of immunosuppressive protocols in use today, and these dosages are quickly tapered to 5 mg/kg in the first few months following transplantation. Drug interactions are significant risk factors for cyclosporin nephrotoxicity.[2]

3. CHRONIC RENAL FAILURE

Long-term use of analgesics, particularly NSAIDs, acetaminophen, and aspirin together, can cause papillary necrosis, chronic renal failure, and chronic interstitial nephritis. In the US, 1% to 3% of cases of end-stage renal disease are linked to analgesic-induced nephropathy. Over the course of many years, the majority of individuals with this condition had used more than 2 to 3 kg of analgesics. Patchy necrosis of the loop of Henle and medullary interstitium are signs of the primary injury in the renal medulla. A biopsy reveals tubular atrophy, interstitial fibrosis, and sporadic mononuclear cells. Papillary necrosis is believed to be caused by altered medullary circulation brought on by salicylates or other NSAIDs that block prostaglandins, which
in turn cause vasodilator prostaglandins to inhibit medullary ischemia and cause tissue damage. Long-term use of transplant medicines, including cyclosporine and FK-506, may cause chronic interstitial fibrosis and renal failure even at appropriate levels, just like analgesics do. Striped interstitial fibrosis and tubular collapse are possible outcomes of an obliterative arteriolopathy. Rejection and clinical diagnosis are not the same thing. To rule out indications of acute or chronic rejection, a renal biopsy is required.[5] Long-term usage of lithium for the treatment of manic-depressive condition has also been demonstrated to result in interstitial fibrosis. Nephrogenic diabetes insipidus is another condition that lithium can cause. It operates at the cyclic adenosine monophosphate second messenger site, enters the collecting tubular cells through the sodium channel, and reduces the ADH sensitivity of the collecting tubules.[5]

4. PSEUDO RENAL FAILURE

By competitively inhibiting tubular creatinine secretion, several drugs, including trimethoprim and cimetidine, can mimic ARF and cause a rise in serum creatinine. Levodopa, flucytosine, and cefoxitin are a few more drugs that may cause problems when determining creatinine levels in the lab. However, in many cases, the elevations in serum creatinine are moderate, non-progressive, and unrelated to abnormalities in urine sediment. Even in the absence of renal impairment, steroids and tetracycline cause a hypercatabolic reaction that raises BUN levels. Care must be used when interpreting the data because a number of these drugs have the potential to induce real acute renal toxicity.[5]

BIOMARKERS FOR THE ASSESSMENT OF NEPHROTOXICITY :

The creation of novel biomarkers is required for the early detection of nephrotoxicity. Biomarkers are biomolecules that indicate the connection between illnesses and external harmful chemicals. In general, biomarkers let us identify the early health harm brought on by exposure to exogenous toxic chemicals and offer insight into how these toxicants start to negatively impact particular populations or people. Finding biomarkers that can be detected in blood or urine as a result of nephrotoxicant exposure is a promising strategy. Urine in particular is thought to be a particularly appealing and effective sample due to its non-invasive nature and ease of collection in large quantities. Prospective biomarker candidates have been found for nephrotoxicity assessment. Some of them have been proven to be potential candidates for the diagnosis of nephrotoxicity, despite the fact that some of them are unable to confer specificity and sensitivity of biomarkers.[1]

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