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ACUTE KIDNEY INJURY (AKI) NEW THERAPIES

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ABSTRACT

This review was set up to open a new prospect in the medical field, trying to cure a crucial clinical issue, with high mortality rates. "Acute Kidney Injury" (AKI), known formerly as "Acute Renal Failure" (ARF). These terms describe a quick decline in kidney function. Clinical therapies that have been used in the last five years was inducing an AKI or had uncompleted or ongoing research. That's why some studies started animal experiments, Followed the known incidence Mechanisms for this disease. An off-label use for some drugs with contra-mechanisms, low-price, and worldwide availability, showed a significant reclaim of renal functions, in a histological assessment for animal AKI models.

KEYWORDS: Acute Kidney Injury, Acute Renal Failure, renoprotictive.

INTRODUCTION

"Acute Renal failure" (ARF) was first termed in (1951) by *"Homer W. Smith"*. This term (ARF) has been widely used over the past 70 years[1,2], to describe an abrupt decline in kidney function, manifested by severe azotemia and often by oliguria or anuria[1], followed by a high mortality rate of more than 50 percent.[3,4] The lack of uniform diagnostic or clinical criteria has made it challenging for researchers to study the incidence, prevalence, and clinical relevance of ARF[2], resulting in multiple different definitions. A (2002) survey revealed at least thirty-five definitions in the scientific literature.[1,5] To remedy the situation, the *"Acute Dialysis Quality Initiative" (ADQI) group* convened a consensus conference in (2002) to develop the first global interdisciplinary consensus criteria for a diagnosis of ARF[1,6], this

criteria was published in (2004), as the *(RIFLE)* system (*"Risk, Injury, Failure, Loss, and End-stage kidney disease"*)[2,5], accompanied by the preferred term *"Acute Kidney Injury" (AKI)* replaced the old one (ARF)[1,5,7-9], brought (AKI) back to the light, after the first time use by *"William MacNider*" in (1918) in a situation of acute mercury poisoning.[1] Alteration of these terms highlighted the actuality that failure and function loss is preceded by a physiological and structural renal injury.[5,6] Later, in (2007), the *"Acute Kidney Injury Network" (AKIN) group* suggested a modified version of the (RIFLE) criteria, which aimed to enhance the sensitivity of AKI diagnostic criteria.[1,5,6] The latest classification of AKI suggested in (2012) by the *"Acute Kidney Injury Working Group"* of *KDIGO ("Kidney Disease: Improving Global Outcomes"),* is based on the two prior classifications were intended to unify the AKI definitions.[1,5]

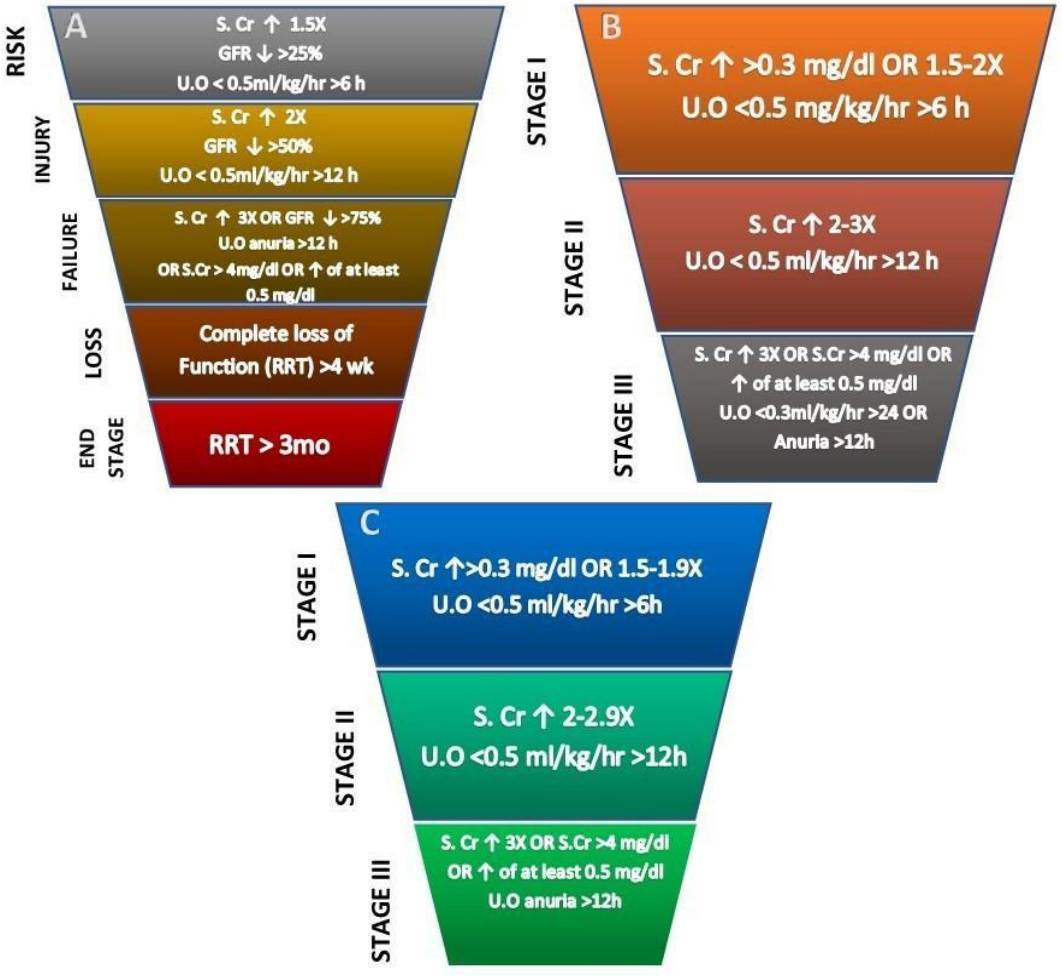

Figure 1

(Figure 1.) Differences between the parameters of the (A) "Risk, Injury, Failure, Loss and End Organ" (RIFLE), (B) "Acute Kidney Injury Network" (AKIN), and (C) KDIGO criteria

for AKI. glomerular filtration rate (GFR), renal replacement therapy (RRT), serum creatinine (S.Cr), urinary output (U.O).[10]

Aetiology[1,11]

Traditionally, the etiology of AKI was divided into 3 categories: pre-renal, urinary organ, and post-renal. The combination of pre-renal and urinary organ causes of AKI is common, for example, in infection or cardiac surgery. Drugs associated with AKI are, among others, nonsteroidal anti-inflammatory drugs (NSAID), many antimicrobials, and a number of other chemotherapeutic agents. The relation among "angiotensin-converting enzyme inhibitors" (ACEIs), "angiotensin receptor blockers" (ARBs) and AKI in patients whose subject surgery is dialectical. Some studies have found increment risk, while others showed no risk when other studies found a decreased risk of AKI among treated patients. Drug-induced AKI will, in most cases, be eased by exchange the toxic drug with an analogous less-nephrotoxic drug, or dynamic administration practices. In patients undergoing cardiac surgery, between 1% and 50% is the incidence of AKI depending on the kind of procedure and also the classification criteria of AKI. AKI is common in patients with sepsis, and patients with septic shock also AKI have an almost doubled in-hospital mortality.

Pre-renal AKI

Pre-renal AKI occurs because plasma flow and intraglomerular pressure is inadequate to keep up filtration capacity. The most common reason is hypovolemia, followed by a decreased cardiac output or impaired autoregulation (The kidneys receive up to 25% of the rate of flow), which can be induced by NSAIDs. Pre-renal AKI is typically reversible in terms of normalizing baseline S.Cr, but might still implicating an injury.

Renal AKI(Intrinsic)

Typically, four core renal structures are involved, well those are "tubules, glomeruli, the interstitium, and intra-renal blood vessels". "Acute tubular necrosis" (ATN) is the term won't to designate AKI resulting from damage to the tubules. it's the foremost common style of intrinsic kidney injury. After glomerular damage, AKI occurs in severe cases of acute glomerulonephritis (GN). The injury to intra-renal vessels reduces renal perfusion and diminishes GFR, cusses vascular damage to end in AKI. Eventually acute interstitial nephritis occurs because of an allergy to a spread medication or an infection.

Post-renal AKI

Post-renal AKI is caused here by an obstruction of urinary flow, which increases intra- tubular pressure and thus, decreases GFR. Additionally, acute tract obstruction can give rise to impaired renal blood flow and inflammatory processes that also contribute to diminished GFR. A number of causes exist as benign prostatic hyperplasia(BPH), urethral stricture, pelvic, or abdominal cancers, neurological causes as multiple sclerosis(MS), ureter obstruction from kidney stones or ureter injury following surgery or trauma.

Combination of pre-renal and renal AKI

In many cases, pre-renal and renal AKI exist at the same time. AKI may happen in sepsis, although the absence of hypotension. The causes are multifactorial including sympathetic activation, hormonal, and inflammatory mediation. In additionally Concomitant pre-renal and renal AKI is observed in disorders like rhabdomyolysis and hypercalcemia, which severe hypovolemia combined with the toxic impacts of calcium and myoglobin causes AKI. Rhabdomyolysis is often related to hypovolemia, thus resulting in pre-renal AKI, direct nephrotoxic effects of myoglobin, heme proteins, and might also lead to the formation of "intraluminal cast and tubular obstruction". After cardiac surgery, the causes of AKI are often a mix of ischemia, inflammation, hypotension, embolism, and free hemoglobin from blood transfusions.

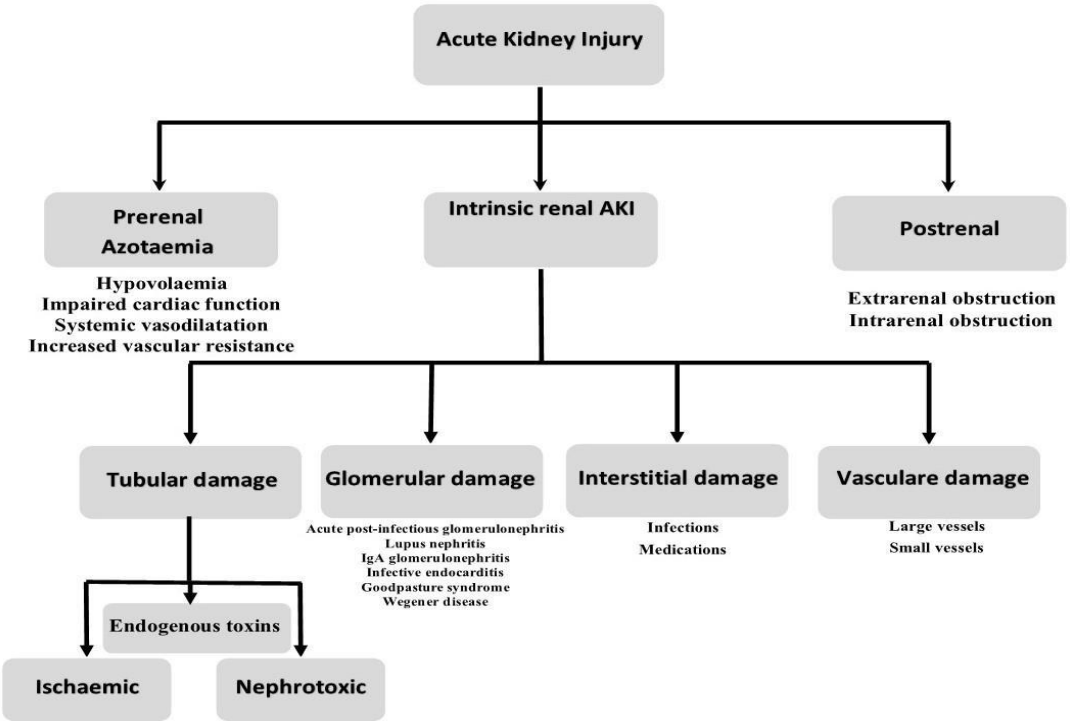

Figure 2

(Figure 2) Aetiologies of acute kidney injury.[1]

ACUTE KIDNEY INJURY MODELS[12]

Recently, several reviews of accessible models, including their advantages and drawbacks, have been; however, the kinds of models are incomplete and lots of details, like model techniques and modeling time, aren't mentioned. Current AKI models are often induced by ischemia-reperfusion (IR), injection of medicinal products, toxins, or endogenous toxins (sepsis-associated AKI), and getting to (post-renal AKI) as ureteral clogging.

Experimental AKI models

Typically known as four main classifications.

Sepsis-associated AKI (SA-AKI)

(SA-AKI) is recognized by high mortality and morbidity due to the intense inflammatory complications. Frequently utilized experimental models of SA-AKI are oftentimes divided into two types: (1) injection within the peritoneum or blood of bacteria or endogenous toxins (e.g. LPS), and (2) intestinal excreta release by ascendens colon stent or cecal ligation and puncture (CLP).

LPS models

lipopolysaccharide (LPS)-mediated AKI has mainly been studied in mice and rats. Compared with other species, rodents are significantly more proof against the toxic, or lethal effects of LPS. The dose of LPS commonly utilized in research is 10–15 mg/kg. After LPS interacts with specific receptors like "Toll-like receptor-4" (TLR-4) on host immune cells, inflammatory cytokines like IL-1, TNF-α, and IL-6 are secreted, resulting in hemodynamic alteration, widespread inflammation, and sepsis. This is often an acute model that typically terminates at 72–96 h.

CLP model

The CLP model is the most often used model because of its simplicity. The first step, is forming ligation of the cecum from the distal to the valve. Then two punctures are made to extrude feces into the sinus. In mice, CLP can evolve the standard symptoms of bacterial peritonitis spotted in humans and yield good outcomes. However, the extent of sepsis and, thus, the variations in age and strain in CLP models are difficult to control. Moreover, reproducible AKI cannot be developed during a CLP model. Although experimental models

have broadened our understanding of sepsis and sepsis-associated AKI, there's still no effective clinical therapy. Several clinical trials targeting specific signaling pathways supported convincing leads to murine models have didn't improve survival in septic patients.

Ischemia-reperfusion (IR)

A current model, it is the most used in general model for renal-transplant studies and clinical AKI. Among the variability of existing models, the mouse clamping model is commonly applied thanks to its low costs, and selection of transgenic models. consistent with previous studies, commonly used models contain bilateral renal IR and unilateral renal IR. First, 50–60 mg/kg of pentobarbital (5 mg/ mL) is employed to anesthetize mice by intraperitoneal (i.p.) injection, with body temperatures then maintained at "36.5–37 °C during surgery". Second, micro-aneurysm clips lock the artery and vein for a variable period of time to induce varying severities of renal injury. generally, ischemia-reperfusion injury is induced by using renal pedicle clamping for 30 minutes. Successful ischemia will be proven by piecemeal darkening of the kidney (from red to dark purple). The clamp is then removed at the specified time to realize reperfusion with the kidney color immediately reverting to red. IR will trigger apoptosis, tubular cell necrosis, oxidative stress, and inflammation, which may lead to a decline of renal function, as evaluated by "blood urea nitrogen" (BUN) and "serum creatinine" (S.Cr).

Obstructive AKI

Unilateral ureter obstruction (UUO) is the commonest rodent model accustomed study AKI and CKD (Chronic Kidney Disease). This model may result in hydronephrosis and blood flow changes. Ischemia, hypoxia, and oxidative stress contribute to the tubular necrobiosis, followed by interstitial inflammation. Additionally, transformed fibroblasts can interact with extracellular matrix deposition leading to renal fibrosis. Recent studies using the UUO model has shown that adenosine levels, nuclear "factor-erythroid-2- related factor 2" (Nrf2), interleukin-10, and therefore, the JAK/STAT signaling pathway are associated with renal fibrosis, thus offering a possible therapeutic target for renal injury. The UUO model is comparatively straight forward. Male animals, which are recommended during this model, undergo a mid-line abdominal incision under anesthesia, with the left ureter then ligated with 4–0 silk. The obstruction to the ureter is removed after 24. Unlike the entire UUO layout, a partial UUO is made by inserting the ureter into a surgically created tunnel within the psoas muscle. Reversible partial UUO is usually performed in neonatal mice to research renal

recovery after obstruction. However, the whole UUO model is more common because it's more easily reproduced and less technical.

Toxin-induced AKI

Those are either drugs or exogenous poisons, while endogenous toxins are accustomed to prompt AKI by their side or poisoning effects. Amongst these models, 6–20 mg/kg of cisplatin might end up in acute tubular injury within 72 h, while 40–200 mg/kg of gentamicin in rats for 4–10 days can induce acute nephrosis. Aristolochic acid and a high dose vitamin B9 (Folic Acid) are frequently accustomed to study AKI- CKD transition, with AKI models developed by glycerol (glycerine) and warfarin are also used.

Cisplatin-induced AKI

Cisplatin could be a chemotherapy agent that's widely utilized in the treatment of solid tumors. However, high doses of cisplatin can induce nephrotoxicity in humans. Direct proximal toxicity to the tubular is critical among cisplatin adverse effects. Tubular cell necrosis and apoptosis are mediated by oxidative stress, inflammation, and calcium overload. These modes of death both result in increased vascular resistance and decreased GFR. Both of The pathology and healing phases of cisplatin-induced acute kidney injury models are comparable to those of humans. Many studies have notified that (6–20 mg/kg of cisplatin) as single Intraperitoneal (i.p.) injection can stimulate AKI within 72 h in rodent models. Furthermore, injecting higher doses of cisplatin have evolved AKI in some groups models, including 30 mg/kg, 40 mg/kg, (i.p.) supported results from this experimental model, several therapeutic targets are established.

Aristolochic acid nephropathy

It has been reported that (i.p.) injection of aristolochic acid (AA) (5 mg/kg/d for 5 days) can induce AKI. The acute aristolochic acid nephropathy (AAN) pathology involves proximal tubular cell injury and necrosis with oxidative stress and progressive interstitial renal fibrosis. Rabbit and rat models were first accustomed to recapitulate human CKD and confirmed that aristolochic acid is said to Chinese herb nephropathy and Balkan endemic nephropathy. Lately, studies on AA in AKI-CKD transition have increased. Signaling pathways like a nuclear factor erythroid 2-related factor 2 (Nrf2) and Jun N-terminal kinases (JNK) signaling are shown to play important roles in AA- induced acute kidney lesions, thus providing a several, new therapeutic targets.

Folic acid-induced AKI (FA-induced AKI)

A high dose of vitamin B9 (Folic Acid) may induce AKI in mice. Intraperitoneal injection of 250 mg/kg of FA (dissolved in 0.3 mmol/L NaHCO3) can cause acute renal toxicity and injury in rats. The mechanism of FA nephropathy may well be because of FA crystal deposition within the tubular lumen, which ends up in obstruction, and extensive necrosis. Mitochondrial dysfunction and early renal fibrosis also, which are associated with CKD pathology, are often found within the FA-induced AKI model, thus, providing a surrogate way during which to investigate the transition of AKI to CKD. A recent study showed that ferroptosis inhibition can protect the kidneys against FA-induced AKI.

Warfarin-induced AKI

Warfarin-induced hematuria AKI is a new paradigm of supported 5/6 renal nephrectomized rats for the examination of (WRN) "warfarin-related nephropathy" examination in exaggerated anticoagulant patients. The 5/6 nephrectomy was performed in Sprague Dawley rats, where warfarin was given orally via drinkable, after three weeks of respite. Extensive glomerular hemorrhage and tubular obstruction in rats may occur after seven days of 0.4 mg/kg/d warfarin administration. Moreover, as the serum creatinine increased. In addition, WRN can even induce AKI, speed up CKD, and increase the death rate in patients treated with warfarin. anywise, the mechanism and therapeutic strategies to ameliorate WRN-induced AKI remain to be demonstrated.

Gentamicin nephropathy

Gentamicin is an aminoglycoside antibiotic commonly accustomed to prevent gram- negative bacterial infection. Regrettably, it had a nephrotoxicity effect, which limited its use in clinical practices. Doses of gentamicin starting from 40–200 mg/kg administered for 4–10 d can induce acute kidney disease in rats. Administration of (100 mg/kg i.p.) for five d is usually recommended mimicking gentamicin-induced nephrotoxicity. This acute model is characterized by elevated levels of creatinine and serum urea, reduced GFR, lesions of the tubules, and fibrosis.

Contrast-induced acute kidney injury (CI-AKI)

CI-AKI also, famous as "contrast-induced nephropathy" (CIN). CIN is a vital consideration in patients undergoing cardiac catheterization. It can occur in patients receiving iodine-based "radiocontrast material" (RCM), especially in patients with preexisting renal problems or the utilize of huge RCM doses. RCM like (Visipaque, Iovist, Ioxaglate, Ioxilan, Iomeprol,

Iopromide, Iohexol, Ioversol, Iopamidol, Iobitridol, Diatrizoate, Metrizoate, Iothalamate) forms the three generations (hyperosmotic: HOCM), (low-osmolality: LOCM), (isosmotic: IOCM). CI-AKI is the third most prevalent cause of hospital-acquired AKI, also is responsible for about 10–12 percent of the cases. RCM administration is often unavoidable in patients with a high risk of CI-AKI, such as pre-existing kidney problems or the use of high doses of RCM, which underscores the requirement for effective prevention strategies.[13] There is no prophylactic or therapeutic agent adopted for CIN available, while the precise mechanisms causing this condition have yet to be completely elucidated.[14] Therefore, different types of rodents, such as mice, rats, and rabbits, are widely used in CI-AKI science.[13]

Male Albino Wistar rats were the model where the induced injury was performed. Rats were allowed free access to water and a standard rat diet. 24 hours after water deprivation, an initial renal injury was induced in males by intramuscular (i.m) injection of glycerine (25%) at a sole dose of (10 mL/kg) semi-dose into each hind limb. (350 mg I/ml) of Iohexol was injected at a single dose of (8.6 ml/kg) over a period of two minutes through the animal's caudal vein, after 24 h of glycerine injection.[14]

Glycerol-induced AKI

Rhabdomyolysis may be a syndrome within which the breakdown of striated muscle results in the discharge of intracellular proteins and toxic compounds into circulation.[12] rhabdomyolysis contributes to the filtration of myoglobulin into renal tubules, which creates obstructing tubular casts. Rhabdomyolysis thus induces acute necrosis of the tubules (ATN). Myoglobin also results in intra-renal vasoconstriction due to scavenging of the nitric oxide and hypovolemia. Rhabdomyolysis is known to cause a wide variety of disorders including intrinsic muscle dysfunction ("including trauma, burns, intrinsic muscle disease, and excessive physical exertion), infections, hypoxia, toxins, medications, metabolic disorders, high temperature, and idiopathic disorders.[4] AKI may be a common complication in 10-40 percent of rhabdomyolysis patients and accounts for the high mortality.[15] The two main causes of RI-AKI are currently oxidative damage and inflammation to breed the standard human symptoms.[12]

To induce the injury, rats or mice are bereft of water for twenty-four h, after which an 8–10 mL/kg dose of fifty percent glycerine is administrated within the hindlimb muscle.[12]

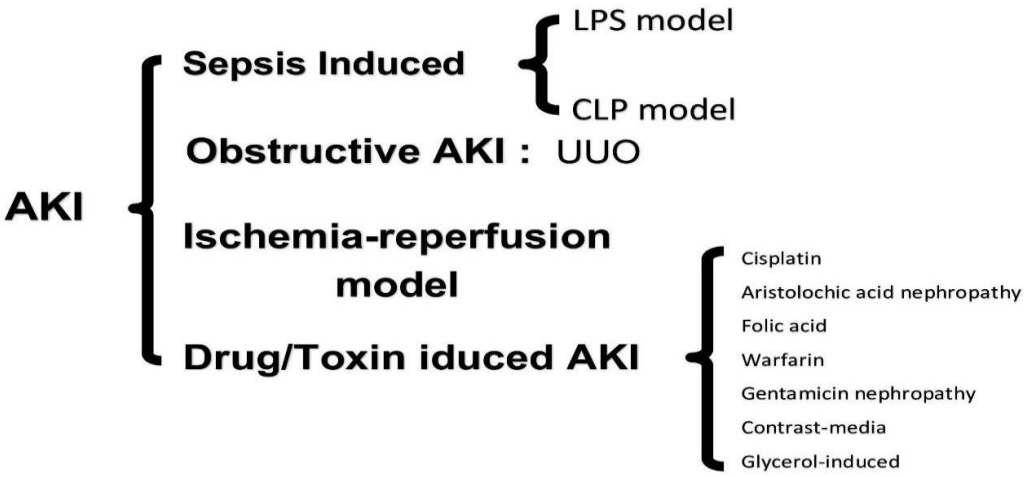

Figure 3

(Figure 3) Summary of major acute kidney injury (AKI).[12]

Clinical interventions

Medical efforts were exerted from the middle of the twentieth century, in order to find AKI cure, insufficient treatments urged the researchers to investigate interventions that showed effects on the kidney, and those are the drugs that showed acceptable results in the last five-years.

EA-230[16]

One of the initial and most frequent manifestations of organ failure in systemic inflammation-related conditions (Infectious, non-infectious) is the development of acute kidney injury (AKI), also it happens in over a half critically ill-patients.

EA-230 A linear oligopeptide immunomodulatory coined of ("Alanine-Glutamine- Glycine-Valine"), derived from the β-chain of the human chorionic gonadotropin hormone. 90 mg/kg/h of EA-230 in a randomized clinical trial (RCT) resulted in reduced levels of proinflammatory mediators in the 180 patients, particulary "IL-6 and IL-8", among others to prevent AKI.

Gemigliptin[17]

gemigliptin is an oral hypoglycemic, interferes by blocking the enzyme Dipeptidyl peptidase-4 (DPP-4) inhibitor. Baek et al, tentatively suggest in their phase II trial that (100 mg/day) of gemigliptin (two times higher than the dose used in the treatment of diabetes) could reduce the cisplatin-induced AKI incidence by 60 % of 91 participants who took gemigliptin.

Iloprost[18]

A prostacyclin (PGI2) analog, synthesized from arachidonic acid released from phospholipids. It is hypothesized to increase the production of cyclic adenosine monophosphate and also the flux of potassium into cells with a decrease in calcium influx, leading to a lowering of smooth muscle cell proliferation and increased dilation. The study has shown a reduction in the incidence of CIN in the coronary angiography setting, by 68%. Demanding larger studies to investigate the effectiveness of Iloprost infusion in preventing CIN, allowing clinicians to better determine safety.

Sodium–glucose cotransporter2 (SGLT2) inhibitors[19-21]

A new oral class of antidiabetic medications inhibits SGLT2-transporter in the proximal tubule of the kidney, Increases the excretion of urinary glucose, and reduces serum glucose. This class includes (canagliflozin, dapagliflozin, empagliflozin). Treatment with SGLT2 inhibitors lowered the risk of acute kidney injury by 25%, but Acute kidney injury (AKI) events, both serious and non-serious, were reported changeably across individual trials.

Statins[22-25]

It's a ("3-hydroxy-3-methylglutaryl-coenzyme A") HMG-CoA reductase inhibitor group, cholesterol-lowering agents. Statin therapy considered to be the backbone of cardiovascular disease (CVD) prevention or care. In clinical practice, some studies have shown that it might protect from contrast-induced AKI (CI-AKI). Two high- intensity statins (Atorvastatin 10-80 mg, Rosuvastatin 20-40 mg) were administrated, while other studies reported that high potency statins are associated with a raised AKI rate.

Toward the new therapies

Due to the high mortality rate of AKI being a critical worldwide clinical case, and the lack of effective therapies, lately, studies continued cure's searching. Some studies have initiate animal experiments using drugs that have shown renoprotective effect, fortunately, these interventions have an acceptable price, worldwide availability. Two mechanisms have utilized to induce AKI, the first one is glycerol causing rhabdomyolysis, provokes (ATN) and leads to AKI, while the other mechanism is the contrast-media (CM) induced AKI.

Ketotifen

Mast cells (mastocyte) distribute very sparsely in the renal under Standard circumstances, and the number of these cells raises enormously during renal IR injury, stimulating the release of

many mediators, such as histamine, trypsin-like enzyme, chymase, heparin, and a host of cytokines, these mediators contribute a wide biological impacts range. that's lead to oxidative damage and promote the production of "reactive oxygen species" (ROS), which reduce the activity of "superoxide dismutase" (SOD) and increase "malondialdehyde" (MDA) levels, resulting in rhabdomyolysis.

Ketotifen is a "histamine H1-receptor antagonist" used to treat allergic disorders, including asthma and eczema[26,27], with a dosage of (1-2 mg BID/P.O.)[28] The principal of pharmacological effects primarily includes preventing the release of chemical mediators from mast cells and other inflammatory cells and suppressing its impact on the organ where it will act. Also, mastocytes are usually distributed in natural connective tissues, mainly located primarily adjacent to blood and lymphatic vessels, nerves, and epithelial surfaces like skin, also located in the respiratory organ, and the alimentary tract, which lead to worse complications. Rhabdomyolysis-induced myoglobinuric AKI (RIAKI) stimulated in Wistar rats by (i.m) injection with glycerine (10 ml/kg of body weight) 50% (vol/vol). The result showed that Glycerol injection caused a marked increase in serum creatinine and blood urea levels. While (2 mg/kg/day, P.O.) Ketotifen significantly reduced the serum creatinine and urea levels, as well as the macroscopic and histological findings, showed the healing effect.[26,27]

Methylsulfonylmethane (MSM)

MSM also recognized as "dimethyl sulfone" and "methyl sulfone", an organic compound of sulfur produces naturally. MSM might have "anti-inflammatory" roles, "chemo-preventive" properties, prostacyclin-inhibiting synthesis (PGI2), "anti- atherosclerotic" action, beneficial effects on "eicosanoid metabolism", and it's scavenging role for free radical. In addition, it is recognized as a potent antioxidant/anti- inflammatory compound. Methylsulfonylmethane compound is one of the least toxicity in biology and is similar in water toxicity. MSM is found in small quantities in many foods, including unpasteurized milk, grains, meat, eggs, bovine milk, fish, and present in human urine, human plasma, and "cerebrospinal fluid" (CSF).[3,4] Commonly is given as (1 to 3 g/day), although 750 mg per day used for arthritis and other conditions.[29] RIAKI induced in Wister rats by intramuscular administration of glycerine 10 ml/kg (50% vol./vol. in saline). (400 mg/kg, P.O.) MSM administration showed a significant decrease in serum levels of urea and creatinine levels, after the increased of their levels, also to the macroscopic and histological Results that showed the curative effect.[3,4]

OLMESARTAN

The kidneys have all the components of the "renin-angiotensin-aldosterone system" (RAAS), which plays an important role in the cardiovascular system. Receptors for angiotensin II (ANG II) also exist in adult human kidneys. ANG-II induced function contributes to vasoconstriction, reabsorption of sodium and water, as well as increased cellular hypertrophy, proliferation, and deposition of the extracellular matrix in the kidney. Rhabdomyolysis-associated renal vasoconstriction is associated with the activation of the (RAAS). Another function in vasoconstriction is the imbalance that controls the renal blood flow between vasoconstrictors and vasodilator products. Renin-angiotensin blockers may have stronger effects as reno-protection than other groups of antihypertensives. In addition, ARBs have been found to delay progression from microalbuminuria to macroalbuminuria in diabetic patients and decrease the incidence of end-stage renal disease in diabetic nephropathic patients.[30] Olmesartan, which is an oral (ARBs), comes in doses of 5 mg, 20 mg, or 40 mg.[31]

RIAKI was provoked by intramuscular injections of 50% (v/v in sterile water) glycerol (10 mL/kg, IM) in the hind limbs of Wistar rats. Al Laham proved the renoprotective effect of (3 mg/kg/day, P.O.). Olmesartan, which could reduce the serum urea and creatinine levels significantly, after their increment due to RIAKI, as well as the macroscopic and histological Results that showed a curative effect.[30]

Pioglitazone

Pioglitazone, which is an anti-diabetic agent in doses (15-30 to 60 mg / d, P.O.)[32], works to reverse almost all pathogenic mechanisms including renal vasoconstriction, tubular obstruction, and direct myoglobin-induced cytotoxicity[15], as well as the (CIN). The precise mechanisms underlying this condition have not yet been completely elucidated but are likely to require the interplay of multiple effects on renal tubules including renal hypoperfusion and medullary ischemia. The direct toxicity of the tubular cells that the contrast medium molecules exert also plays an important role. ROS were also involved as contributing factors. In pathophysiology, the inflammatory process is also particularly important.[14] Pioglitazone is classified as a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist (a thiazolidinediones member), which links to a specific site on the "DNA helix". This controls the transcription of various target genes and participates in the control of many critical processes such as adipocyte discrimination and metabolism of both "carbohydrates and

lipids". Acute Kidney injury was induced in male Albino Wistar rats by intramuscular injection of 50% glycerol(10mL/kg)[15], whereas in the other study adopt the (CIN) mechanism used "Iohexol as contrast-media (CM) (350 mg I/ml) at a single dose of 8.6 mL/kg s injected through animals caudal vein, Preceded by intramuscular injection of Glycerol 25% at a single dose of (10 mL/kg)".[14] (10 mg/kg/day, P.O.) Pioglitazone showed a reno-protective effect, and it could reduce the serum urea and creatinine levels significantly, after the increment in their levels, caused by the induced injury. The macroscopic and histological results showing the curative effect, too.[14,15]

CONCLUSION

AKI or ARF still a grave common problem without an appropriate medicament. The high death-rate demand a rapid solution, and that gives the previous studies priority to initiate the clinical phase quickly, in addition to the renoprotective effect, their price is acceptable, and they are available globally, which opens a new prospect to enhance the healthcare field.

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