Most important cellular changes involved in renal ischemia reperfusion Injury and the consequent impact on selected remote organs

Abstract: Because of the high rate of baseline oxygen use by renal cells, kidney is highly influenced by obstruction of arterial blood inflow and subsequent shortage of the received oxygen, this condition is known as Ischemic injury. There are many clinical settings associated with unavoidable ischemic state such as kidney transplantation, partial nephrectomy or suprarenal procedures of the aorta. During ischemia many cellular changes occur including vascular congestion and adhesion of inflammatory cells to the endothelium with subsequent infiltration into the kidney tissue. Following ischemia, a phase known as Reperfusion begins and involves a return of blood and oxygen supply to microvessels. Reperfusion was expected to restore the damage occurred during the ischemic phase, Paradoxically, Reperfusion leads to more congestion, red cells trapping and excessive generation of reactive oxygen species (ROS), which can oxidatively modify significantly every type of biomolecule, thereby inducing cell dysfunction and induce reperfusion injury. Ischemia reperfusion injury (IRI) is also related to a phenomenon called Remote Organ Injury (ROI) in which the damaging effect induced by I/R is not only restricted to the tissue that undergoing the initial ischemia but also it leads to injury to remote organs such as the liver ,lung , gut. ROI usually occurs by the same mechanisms seen in the local injury induced by I/R including the generation of ROS, leukocytes, and inflammatory mediators (e.g; TNF-α). These substances are directly released from the primary injured tissue or indirectly from activated leukocytes or other inflammatory cells causing organ dysfunctions in distant organs.

Key words: *Renal ischemia-reperfusion injury reactive oxygen species (ROS) - Inflammatory response- Remote organ injury.*

Introduction:

The functions of the kidney are vital to life and are regulated by the endocrine system by hormones such as antidiuretic hormone (ADH), aldosterone, and parathyroid hormone (PTH). The important functions that the kidneys serve including:[1]

1. Filtration and excretion of metabolic waste products
2. Regulation of necessary electrolytes, fluid, and acid-base balance
3. Controlling reabsorption of water and maintaining intravascular volume ,also kidneys reabsorb glucose, amino acids
4. Stimulation of red blood cell (RBC) production.
5. Regulation of blood pressure via the renin-angiotensin-aldosterone system,
6. Hormonal functions via erythropoietin, calcitriol, and vitamin D activation.

The kidney is considered as the most important organ for the excretion of water soluble drugs and/or their metabolites in to the urine.[2]

Nephrons are urine-producing functional structures of the kidney [1] which are distributed at the cortex and medulla. A normal human kidney contains 800,000 to 1.5 million nephrons.[3] Each nephron is composed of:

- The renal corpuscle (Bowman capsule): containing the glomerulus.
- The Proximal convoluted tubule (PCT), located in the renal cortex.
- loop of Henle (LOH) :descending limb and ascending limb located in renal medulla
- The distal convoluted tubule.
- Collecting duct
- **Cortical nephrons** have their loop of Henle in the renal medulla near its junction with the renal cortex.
- **Juxtamedullary nephrons** have their the loop of Henle deep in the renal medulla.[4]

Renal blood supply [5]

Normally, the kidneys receive 1,000 to 1,250 mL/min of blood in the adult person which is about 25% of the cardiac output (COP). This amount far exceeds that needed to provide the kidney's intrinsic oxygen requirement but ensures optimal clearance of all wastes and drugs from the body. Essentially, all blood passes through glomeruli, and about 10 % of renal blood flow is filtered (a glomerular filtration rate GFR of 125 mL/min in the normal adult). The basal normal blood flow is 3 to 5 mL/min/g of tissue, greater than in most other organs.

The vascular structure of the renal cortex is complex. The renal artery enters the kidney at the hilum, where it divides into five interlobar arteries, each an end artery. The afferent arterioles, which arise from the interlobular arteries, divide within the cortical tissue to form the glomerular capillary network. The capillaries then reunite to form the efferent arterioles. Vessels from the efferent arterioles supply the proximal and distal tubules and portions of the loops of Henle and the collecting ducts. The juxtaglomerular apparatus is between the afferent and efferent arterioles and the macula densa, a specialized group of cells which are located in the distal convoluted tubule. The point at which the afferent arterioles enter the glomerulus and the efferent arteriole leaves it, the tubule of nephron return back to touch the arterioles of the glomerulus of the same nephron from which it exists. At this position, thick ascending limb of loop of Henle, there is a specific modified region of tubular epithelium called the Macula densa.

Renal ischemia/reperfusion

Simply the term ischemia means that there is a deficient blood supply to tissues due to obstruction of arterial blood inflow. The body is able to adapt to a reduction in blood flow to a certain level, but when delivery of oxygen and nutrient substrates becomes inadequate, cellular injury leads to organ dysfunction.[6] Kidney is considered as one of the most susceptible body organs to ischemia. Renal parenchymal oxygenation is graded with the highest oxygen levels noted in the cortex, medium levels in the outer medulla, and the lowest levels in the papillae. As a consequence, cortical cells are the most sensitive to ischemia, while cells in the outer medulla can shift to oxygen-independent metabolism making them less sensitive to a hypoxic environment. Inner medullary and papillae cells use predominantly glucose to generate ATP via anaerobic glycolysis. Thus, these regions demonstrate a reduced sensitivity to ischemia. Reperfusion could paradoxically induce and exacerbate tissue injury and necrosis.[7]

Renal ischemia/reperfusion injury (IRI) results from a generalized or localized impairment of oxygen and nutrient delivery to, and waste product removal from, cells of the kidney.[8-10] There is a mismatch of local tissue oxygen supply and demand and accumulation of waste products of metabolism. As a result of this imbalance, the tubular epithelial cells undergo injury and, if it is severe, death by apoptosis and necrosis (acute tubular necrosis [ATN]), with organ functional impairment of water and electrolyte homeostasis and reduced excretion of waste products of metabolism.[10] There are major clinical settings or medication use which may lead to deposition of ischemia reperfusion injury : [6,11]

- Acute renal failure caused by medications for the treatment of hypertension, especially with angiotensin converting enzyme inhibitors (ACEIs)
- Progressive azotemia
- Acute pulmonary edema
- Renal transplantation.
- Medication use : Vasoconstrictive drugs ,Cyclosporine use , Tacrolimus use ,Overuse of NSAIDs and Radiocontrast agents
- Hypotension linked to sepsis or blood loss after surgery and trauma.

- Renal vascular diseases

In the following lines we will discuss the most important cellular changes involved in the ischemia and reperfusion injury. Also the remote organ injury that occurs in the liver following renal ischemia reperfusion will be mentioned.

Cellular changes during ischemia:

One of the most important changes in ischemia are that occur in the endothelium. Lately these changes lead to endothelial dysfunction, these changes include:[12]

a) Changes in the Vascular tone:

Nitric oxide (NO) one of the autacoids that is acting on vascular smooth muscle cells to induce vasodilatation [13]NO is generated by the enzymatic transformation reaction illustrated below and is catalyzed by an enzyme called nitric oxide synthase (NOS)

$$L\text{- arginine } +O_2 \quad NOS \quad L\text{-citrulline}+ NO$$

NOS exists in two different isoforms which both are found in the kidney;[14]

✓ The first isoform is endothelial NOS (e NOS): found in vasa recta, inner medullary collecting duct and glomeruli.[15]

✓ The second inducible NOS (iNOS) can be expressed by vascular smooth muscle cells[16] and immune cells such as monocytes, macrophages, neutrophils[17] in the kidney.

NO which is derived from the enzymatic activity of (iNOS) appears to participate in vascular dysfunction[18] and leading to tissue damage.[19] There are two main pathways involved in the tissue damage produced by NO derived from iNOS:

(i) Peroxynitrite (ONOO-) generation, [20] (oxidant and nitrating agent) . Due to its oxidizing properties, peroxynitrite can damage a wide array of molecules in cells, including DNA and proteins leading to endothelial dysfunction and tissue damage.

(ii) Secondary to endothelial dysfunction and damage, there will be an imbalance of eNOS and iNOS. The relative decrease in eNOS , leading to loss of antithrombogenic properties of the endothelium and increase susceptibility to microvascular thrombosis which leading to further tissue damage.[21]

One of the future approaches is to examine the effect of iNOS inhibitors on the protective effects against ischemia [22]

b) Changes in the microvascular Permeability:[23-28]

The increased microvascular permeability observed in ischemia is likely to be caused by a combination of factors, most of them is due to the activation of matrix metalloproteinase-2 (MMP-2) or matrix metalloproteinase-9 (MMP-9) which leading to Severe alterations in the integrity of the adherent junctions of the renal microvasculature.

c) Changes in the Coagulation process:

The interaction between Endothelial cells through their interaction with protein C and thrombomodulin. Protein C is considered as one of the natural anticoagulants while Thrombomodulin is a protein cofactor expressed on endothelial cell surfaces that modifies the substrate specificity of thrombin

Under the physiological condition, the interaction between thrombin and thrombomodulin leads to the formation of thrombin-thrombomodulin complex which in turn activates protein C. The activated form of protein C (APC) plays an important role in regulating blood clotting, inflammation, cell death and maintaining the permeability of blood vessel walls in humans and other animals.[29]

During an inflammatory response such as in ischemia, decreases in the anticoagulant and anti-inflammatory effects of the protein C pathway occur .that is due to:

- The degradation or decreased production of protein C
- Downregulation of endothelial protein C receptors EPCR
- Decreased thrombomodulin expression,

The microvascular function is compromised, resulting in spreading intravascular coagulation and thrombosis, the local tissue perfusion is decreased, and finally organ dysfunction is developed.[30]

d) Acute epithelial cell injury

It worth to mention that during ischemic injury, all segments of the nephron can be affected, but the most commonly injured epithelial cell is the proximal tubular cell. There are many reasons that make proximal tubular cells are particularly susceptible for ischemic injury:

- Proximal tubular cells have a high metabolic rate and a limited capacity to undergo anaerobic glycolysis.

- Owing to the unique blood flow in the outer stripe of the S3 segment of the nephron, there is marked microvascular hypoperfusion and congestion in this region after injury, which persists and mediates continued ischemia even when cortical blood flow might have returned to near-normal levels.

According to the extent of injury, epithelial cells undergoing sub-lethal or less severe injury will have the capability of functional and structural recovery if the insult is interrupted. While cells that suffer a more-severe or lethal injury will undergo apoptosis or necrosis, leading to cell death.

Moreover, following a reduction in effective kidney perfusion, epithelial cells cannot maintain the adequate intracellular ATP for the essential processes made by the cells. In case of sever reduction in the renal perfusion, cell death by necrosis or apoptosis may occur.

e) Role of Inflammation:

Following ischemic injury, a number of potent mediators are generated by the injured epithelial proximal tubular cell, including proinflammatory cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-6, IL-1β and IL-8.[31]

Early inflammation is characterized by margination of leukocytes to the activated vascular endothelium via interactions between selectins and ligands that enable. Leucocytes interact with the vascular endothelium via a series of distinct steps characterized by leukocyte '*rolling*' on the endothelium, firm adherence of leucocytes to the endothelium and endothelial transmigration.[32] Upon reaching the extravascular compartment, activated leucocytes release toxic ROS, proteases and elastases, resulting in increased microvascular permeability, edema, thrombosis and parenchymal cell death.[33]

In many experimental studies it was shown that the level of both TNF-α and MPO is increased following the ischemic attack so the following points will to illustrate their role in ischemic injury. [34]

Tumor necrosis factor- alpha (TNFα) is a protein hormone produced by systemic leukocytes (primarily by activated macrophages). It has been implicated as a systemic mediator in the development of septic shock and other pathologic conditions. Serum TNF-alpha has also been detected in a variety of cardiac disease states and after ischemia-reperfusion injury.[35]

Neutrophils are the first cells to accumulate at the site of ischemic injury. Blockade of neutrophil function or neutrophil depletion provides only partial protection against injury, indicating that other leukocytes also mediate injury. These inflammatory mediators include macrophages, B cells, and T cells.[36] These cells mediate tubular injury at various phases of the process, and there are synergistic interactions between different cell types.[33] Neutrophils are the inflammatory cells that abundantly produce ROS during IR injury.

Myeloperoxidase (MPO) a heme-containing protein which is found mainly in the azurophilic granules of neutrophils and to a lesser extent in the lysosomes of monocytes in humans; MPO has an important role in the oxidative stress process through catalyzing the formation of hypochlorous acid (HOCl), a toxic agent to cellular components, that initiates

oxidative injury.[37]. MPO is considered as one of the marker of oxidative stress during ischemic conditions. [34]

Oxidative stress is defined as imbalance between reactive oxygen species (ROS) production and the internal antioxidant system. MPO or hypochlorite (or hypochlorous acid HOCl) may further mediate oxidative modification of lipids, proteins and DNA which in turn leading to cell injury and dysfunction.[83]

Before ending this section of the article it worth to mention that Cyclooxygenase-2 enzyme has an important role during ischemia. In some experimental animals including: mice, rats, rabbits, and dogs; it was shown that COX-2 expression in kidney cortex has been localized to the macula densa/cortical thick ascending limb of Henle (cTALH).[39] There was acontroversy about the expression of COX-2 in the human kidney but Studies in humans >60 years of age have demonstrated COX-2 in macula densa[40] and have documented increased macula densa COX-2 in patients with Bartter syndrome (a rare inherited defect in the thick ascending limb of the loop of Henle). It has been suggested that the increased macula densa COX-2 seen in elderly humans may be secondary to decreased basal renin production associated with aging.[41]

In general, COX-1 functions in the control of renal hemodynamics and the glomerular filtration rate (GFR); COX-2 functions affect salt and water excretion, although there is some overlap.[42] In a person with normal renal hemodynamic parameters, prostaglandins (PGs) do not play a dominant physiologic role in maintaining renal blood flow and GFR.[43] However, prostaglandins role become of high importance in a person with compromised renal hemodynamics. In such conditions, vasodilating prostaglandins are synthesized by kidney as an autoregulatory response to offset vasocontricting autacoids and to maintain renal perfusion and GER.[44]

Only PGs derived from COX-1 are involved in normal renal function while COX-2-derived PGs will have different role.[45] Up regulation in COX-2 expression During the inflammatory situation associated with the renal ischemia, COX-2 induction has been demonstrated in several phagocytic cells due to the effect of many proinflammatory cytokines such as IL 1β, TNFα, platelet activating factor PAF. Induction of COX-2 in macrophages involves reactive oxygen intermediates and an increase in prostanoids synthesis which are potent inflammatory mediators that can exaggerate the inflammatory condition.[46] The blockade of COX-2 effect can prevent the subsequent inflammatory cascade. So the use of COX-2 inhibitors is considered one of the treatment approaches for the clinical situation associated with unavoidable ischemic state such as kidney transplantation, partial nephrectomy or suprarenal procedures of the aorta [34]

Cellular changes during reperfusion injury

Following ischemia, reperfusion is unequivocally essential for the survival of ischemic tissues as the reestablishment of blood flow as well as the recovery of tissue oxygenation in the affected area bring indispensable nutrients to tissue repair. Paradoxically, reperfusion of the acutely ischemic tissue may lead to local and systemic complications. Reperfusion of previously viable ischemic tissues may augment tissue injury in excess of that produced by ischemia alone so it is called "oxygen paradox" phenomenon[47]

The Reperfusion injury following ischemia can be mediated by several mechanisms that will be discussed below:

a) Free radical role in reperfusion injury:

Low levels of oxygen radicals and oxidants are normally formed in cells and play important roles in cellular homeostasis, mitosis, differentiation, and signaling. Although mammalian cells express endogenous free radical scavenging enzymes [48], such as superoxide dismutase (SOD), catalase and glutathione peroxidase, these antioxidative defenses are overwhelmed or consumed after ischemia and reperfusion period.

During cellular ischemia ATP is degraded to form hypoxanthine. Under normal physiological conditions, hypoxanthine is oxidized by xanthine oxidase (**XO**) to xanthine using oxygen; therefore during ischemia (a state of oxygen deprivation) it is unable to catalyze the conversion of hypoxanthine to xanthine, resulting in a build-up of excess tissue levels of hypoxanthine. When oxygen is reintroduced during reperfusion, the conversion of accumulated hypoxanthine by xanthine oxidase (XO) results in the formation of toxic ROS (reactive oxygen species) [49] including peroxide anions (O_2-), hydroxyl radicals ($OH-$), hypochlorous acid (HOCl). Owing to their highly reactive nature, ROS generated upon reperfusion can oxidatively modify every type of biomolecule found in cells affecting their function. Another free radical type is also formed called reactive nitrogen species (RNS), which refers to radical molecules derived from NO. The produced free radicals ROS and RNS may interact together and produce more aggressive product called reactive nitrogen oxide species (RNOS), such as strong prooxidant peroxynitrite. Free radical production can be described as a nonstop cascade process the eventually lead to cellular injury.[7]
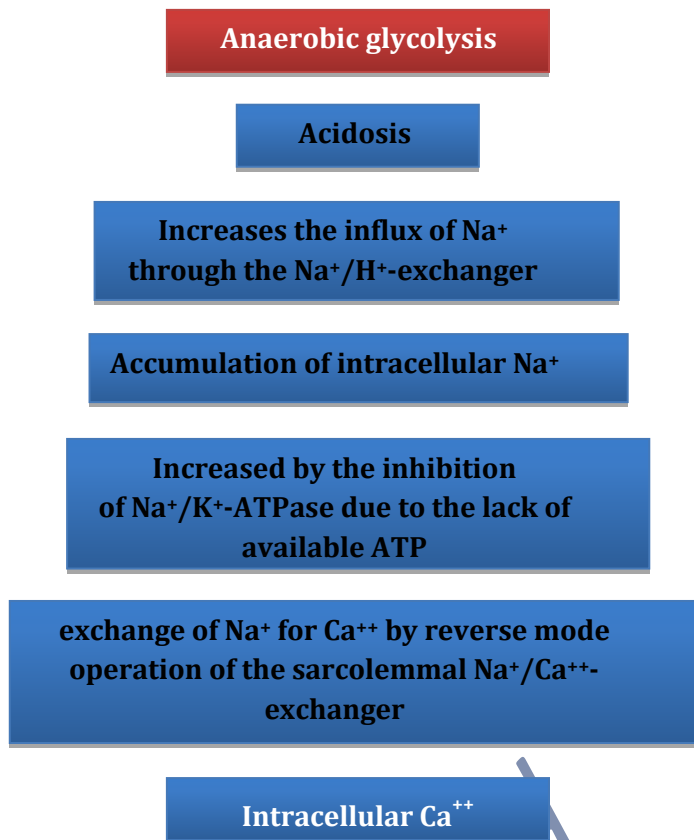
b) pH paradox phenomenon

In the ischemic cells, changes in metabolism occur which include anaerobic glycolysis and the hydrolysis of adenosine triphosphate. These metabolism changes lead to intracellular pH falls. If ischemic cells are reperfused at acidotic pH, cell killing is abrogated. In contrast, the rapid rise in intracellular pH during reperfusion provokes cell killing, this phenomenon is called pH paradox. Reperfusion exacerbates this damage by triggering an inflammatory reaction and disrupts the microcirculation. [50]

c. Calcium overloads

During ischemia as we mentioned above the cells become dependent on anaerobic glycolysis to maintain ATP level in the absence of oxygen supply. Hence, accumulation of lactate and protons causes a fall in cytosolic pH. In an attempt to reestablish normal pH, the cell releases H+ ions out of the cell in exchange for Na+ via the Na+/H+ exchanger (NHE). Then Na+ ions are, in turn, exchanged for Ca2+ by Na+/Ca2+ exchanger .This increase in cytosolic Ca2+ is greatly exacerbated upon reperfusion due to the rapid pH increase and removal of extracellular H+ ions further increases the proton gradient across the plasmalemma, thereby accelerating NHE exchanger function.[7]

In addition Ca2+ reuptake into the calcium stores (endoplasmic /sarcoplasmic reticulum) ER/SR is impaired by I/R. Hence, we reached a state in which there is an increase in the calcium level with inability for the excess calcium amount to be properly stored which leads to lethal elevations in intracellular Ca2+ or calcium overload as illustrated in diagram (1

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┌─────────────────────────────┐
│     Anaerobic glycolysis     │
└─────────────────────────────┘

        ┌───────────────┐
        │    Acidosis    │
        └───────────────┘

   ┌────────────────────────────┐
   │   Increases the influx of Na+   │
   │  through the Na+/H+-exchanger    │
   └────────────────────────────┘

  ┌──────────────────────────────────┐
  │  Accumulation of intracellular Na+  │
  └──────────────────────────────────┘

   ┌──────────────────────────────┐
   │    Increased by the inhibition    │
   │  of Na+/K+-ATPase due to the lack of  │
   │       available ATP             │
   └──────────────────────────────┘

 ┌────────────────────────────────────┐
 │  exchange of Na+ for Ca++ by reverse mode  │
 │  operation of the sarcolemmal Na+/Ca++-  │
 │            exchanger               │
 └────────────────────────────────────┘

        ┌───────────────┐
        │ Intracellular Ca++ │
        └───────────────┘
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Diagram (1): Steps that lead to calcium overload during ischemic injury

Here is a question, what are the consequences of calcium overload; these massive alterations in Ca2+ activate a variety of systems, all of which can contribute to cell death following I/R:

- Lethal increase in Ca2+ is to take it up into the mitochondria via the mitochondrial Ca2+ uniporter. When the elevations in mitochondrial Ca2+ become excessive, they can trigger the mitochondrial permeability transporter MPT response. This leads to mitochondrial swelling and cell death in another word the high cytosolic concentrations of Na^+ and Ca^{++} result in intracellular edema.

- Activation of Ca2+/calmodulin-dependent protein kinases (CaMKs), which also contribute to cell death and organ dysfunction following ischemia.[51]

- **The no-reflow phenomenon[51,52]**

Simply from its words the no reflow phenomenon can describe the capillaries of organs through which the blood did not flow properly after reperfusion. In another words, the no-reflow phenomenon refers to the clinical observation that blood flow to an ischemic organ is often not fully restored following the release of a vascular occlusion. So, no matter now the blood flow is efficiently or rapidly restored to the blood deprived capillaries if microvascular obstruction still exists. During reperfusion a large number of capillaries fail to adequately reperfuse which lead to the evolution of the no reflow phenomenon.

Activated neutrophils play an important role in the development of no-reflow phenomenon. Activated neutrophils are arrested in the capillaries due to the decrease in the driving flow pressure during ischemia and the large size of neutrophils both reasons allow the blockade of the capillaries. Furthermore, as mentioned previously the acidic environment associated with ischemia increases the stiffness of these white cells thereby increasing the likelihood for leukocyte plugging in capillaries. Endothelial barrier disruption associated with I/R leads to transmicrovascular fluid filtration and protein efflux in turn edema forms. When the blood supply is reestablished in reperfusion, restoration of luminal pressures occur and hence the edema formation rate is increased. The fluid accumulates in the ischemic tissues leading to increased interstitial pressure surrounding blood vessels, as a result collapse of the

microvessels occur and produce extravascular compression. This leading to inability of the blood to pass through theses microcapillaries during reperfusion so, the no-reflow phenomenon exists. This extravascular compression mechanism is especially important in tissues that cannot expand during edematous state because they are surrounded by structures that limit expansion such as the brain, many skeletal muscles and the kidney.

Continued organ dysfunction in the post-reperfusion period, failure of a transplanted graft or increased infarct size is all clinical settings that may be explained to an extent by the no reflow phenomenon.

Remote organ injury following renal I/R injury

Untoward effects of I/R are not necessarily restricted to the specific tissue undergoing the initial ischemia. That is, a frequent consequence induced by reperfusion after localized tissue ischemia is injury to other organ systems, so-called distant or remote organ injury (ROI). The ultimate expression of ROI is multiple organ dysfunction syndromes.

As known, renal ischemia reperfusion (IR) is one of the most pivotal causative mechanisms of acute kidney injury (AKI) which is deemed a pan-organ problem that exerts negative impact on many organs of the body [53]. The hypothesis of distant organ injury (lung, heart, brain, liver, etc.) has emerged over the last decade and may demonstrate the reason for the potential negative influence of AKI on outcome [53-55]. High mortality rate during AKI is largely due to this multiple organ dysfunction.

Animal studies obviously indicate that AKI simulates remote organ dysfunction through different particular pathways including apoptosis, inflammatory cascades, differential molecular expression, and induction of remote oxidative stress. [56]

The Proposed underlying mechanism of remote organ injury consequences after AKI could be categorized into four following mechanisms: (1) Classical manner of acute uremic case which affects all metabolic and endocrine pathways, causes disruption of volume and electrolyte homeostasis, and further proximate agents have a profound influence on immune-competence [57,58]; (2) Inflammatory nature of the injured kidneys which may produce clearly higher inflammatory chemokines expression and renal fibrosis [59] as well as oxidative stress by disturbing systemic iron homeostasis [60]. This inflammatory process may eventually transform into systemic inflammatory reaction mediating remote organ injury [61]; (3) A great modulating effect on the remote organ injury would be induced by the disturbance of cytokine/chemokine homeostasis in AKI, which may be attributable to the decreased renal clearance and/or increased production of these cytokine/chemokine [59,60,62]; (4) Healthcare impediment of renal replacement therapy (RRT) support is considered as essential for AKI patients with fluid overload [63]. However, RRT is proven to carry dramatic risks for adverse patient outcome leading to the reactive oxygen species as well as, hemodynamic instability and nutrients loss during RRT and inflammatory reaction [64,65]. Depend on the mechanisms mentioned before; several complex pathways are involved in the remote organs injury during AKI including pulmonary, cardiovascular, gastrointestinal, hepatobiliary, and neuromuscular. [56,66-69]

Remote impact on the heart

Acute kidney injury (AKI) may result in acute cardiac disorder via some mechanisms including: (1) myocardial damage due to neutrophil trafficking, myocyte apoptosis, endothelial dysfunction, as well as elevated level of inflammatory cytokines (IL-1, IL-6, and TNFα resulting from increased production and impaired clearance; (2) increased preload secondary to AKI-induced salt and water retention [70,71]. To illustrate the association between acute kidney injury and cardiovascular risk, Ko et al.[72] revealed that mortality and major adverse cardiovascular and cerebrovascular events significantly correlated with the severity of AKI, and the severity of AKI influences strongly patient outcomes, so it has to be recognized immediately and treated aggressively when possible. Furthermore, the association between AKI and subsequent risk for cardiovascular disorder were identified in other studies [73,74]. A

research study conducted by Kelly [70] showed an increased level of TNF-α and IL-1 in the heart in the 48 first hours after renal ischemia reperfusion. This was accompanied by rise in myeloperoxidase activity in the heart. Furthermore, it is also observed increases in left ventricular end systolic diameter, left ventricular end diastolic diameter, and decreased fractional shortening by echocardiography after renal ischemia reperfusion.

Remote impact on the liver

The underlying mechanisms between acute kidney injury and liver remains to be understood [75]. Evidence showed that AKI has significant effect on liver inflammatory response and drug as well as other nutrient metabolism, and even patient outcomes [67]. Other experimental studies showed that AKI cause increased vascular permeability, T-lymphocyte infiltration, neutrophil in the liver [66]. Moreover, AKI invigorates oxidative stress, upregulate the expression of injury-promoting molecules and decreases antioxidants level leading to tissue damage of hepatocytes [68,54]. In study conducted in Wister Male Rats, hepatic levels of TNF-α and Malondialdehyde increased significantly after renal ischemia reperfusion, while total glutathione decreased, suggesting the activation of oxidative stress). Hepatocytes apoptosis increased in 24 h after nephrectomy. In addition to that, Authors found histological of hepatocyte injury following AKI [54]. Another study conducted on mice showed rapid hepatocyte necrosis, neutrophil infiltration, proinflammatory mRNA up regulation, and vacuolization [76].

Remote impact on the brain

Acute kidney injury has neurological complications including attention deficits, dizziness, seizure, tremor, delirium, altered mental status, and even death [56] soluble and cellular inflammatory cytokines and uremic toxins contribute to the neurological complications. Animal studies using mice showed that AKI may result in augmentation of vascular permeability, increased cerebral proinflammatory cytokines (IL-6, IL-1β, IL-12, and glial fibrillary acidic protein), disruption in the blood brain barrier, and microgliosis (up-regulation of brain macrophages)[56,77]. In addition to that, posterior reversible encephalopathy syndrome and myopathy have been presented in AKI patients with and without hypertension.[78,79]

Remote impact on the lung

Respiratory outcomes are the most clinically connected to Remote organ injury in AKI seen in patients with pulmonary inflammation and mechanical ventilation [56,68]. Acute kidney injury changes peripheral vascular responses by increasing oxidative stress [80]. Several experimental studies revealed that AKI results in pulmonary injury via following pathways: (1) increased production of chemokines and cytokines related to impaired renal clearance; (2) lung edema resulted from increased lung vascular permeability; and (3) increased leukocyte and mononuclear phagocyte production. Additionally, AKI may express modulatory effects that vary with the severity of pulmonary injury [56,81]. Brøchner et al.[82] compared 5 mice (C57BL/6) groups with different subtypes of AKI. This study revealed that Myeloperoxydase production in the lung significantly increased in the groups with acute kidney injury than in limb ischemia and sham groups. Additionally, interleukin (IL)-6 and IL-10 blood levels significantly increased in the AKI groups compared to sham group, suggesting the role of ischemia reperfusion to the systemic inflammatory response. [82]

Remote impact on the Gut

Gut is a new organ which is remotely injured during AKI. The hypervolemia and inflammatory response related to AKI change the permeability of mesenteric vascular membrane and stimulate the formation of intestinal edema leading to sepsis [83]. The underlying mechanisms including: disruption of mucosal integrity, liberation of proinflammatory mediators, increased intestinal permeability, and translocation of intestinal microorganisms. [84]

Conclusion:

Renal ischemia reperfusion injuries have been demonstrated in many clinical settings, such as kidney transplantation, partial nephrectomy or suprarenal procedures of the aorta where ischemia can not be avoided. Several mechanisms are involved in the induction of Renal I/R injury. The most important mechanisms are related to generation of the reactive oxygen species (ROS) and infiltration of inflammatory mediators such as cytokines (tumor necrosis factor alpha (TNF-α)) and interleukins which eventually leading to cell death and loss of cellular functions. Moreover the local injury may spread to other distant organs (heart, brain, liver, lung and gut) and cause multiple organ injury. Each mechanism can be target of therapeutic intervention to protect the kidney and the distant organ from the expected damage occurred as a result of the ischemia and reperfusion injury.

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