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Integrative View of the Mechanisms that Induce Acute Kidney Injury and its Transition to Chronic Kidney Disease

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ABSTRACT

There is ample evidence showing that acute kidney injury (AKI) increases the risk of developing chronic kidney disease (CKD). Although considerable efforts have been undertaken in recent years to elucidate the mechanisms responsible for the AKI to CKD transition, many questions remain to be answered. In this review, we address most of the latest studies elucidating the mechanisms involved in this transition. Based on recent studies, the consensus to date is that endothelial and proximal tubular epithelium injury along with the activation of inflammatory processes occurring after an AKI episode, not only establish a close interrelation but also trigger a series of signaling pathways that culminate in the generation of tubulointerstitial fibrosis and chronic hypoxia, which lead to the progressive deterioration of functional tissue. These events highlight that the tubular epithelium does not appear to be the same after cell damage occurs. In this review, we present the advances aimed at elucidating the mechanisms that lead to a maladaptive response and how sex hormones seem to be involved in a positive or negative adaptive response. Elucidating and characterizing the mechanisms responsible for the AKI to CKD transition are an indispensable preliminary step that will help to identify the most important actors in this process. (REV INVEST CLIN. 2018;70:261-8)

Key words: Renal fibrosis. Hypoxia. Inflammation. Oxidative stress. Maladaptive repair. Tubular cells.

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ACUTE KIDNEY INJURY (AKI)

AKI is generally defined as a clinical syndrome caused by an abrupt reduction in renal blood flow that culminates in the decrease of urine production and the accumulation of toxic compounds. These alterations are observed within several hours or days once the event has occurred[1-3]. AKI is a serious public health problem with high morbidity and mortality, associated with an increased long-term risk of developing chronic kidney disease (CKD)[4]. Moreover, this condition generates an additional cost to health systems and longer hospital stays[5,6]. Unfortunately, the interventions to prevent AKI or to improve prognosis have not been efficient enough. Another difficult issue that clinicians around the world face is the definition and classification of AKI, limiting its precise diagnosis. The current classification is included in the Clinical Practice Guidelines for Kidney Disease: Improving Global Outcomes (KDIGO), which maintained the definition and staging of AKI based on the previous criteria of risk, injury, failure, loss, end-stage renal disease (ESRD), and AKI network. This new classification considers the elevation of creatinine ≥ 0.3 mg/dL in 48 h, or a greater increase of ≥ 1.5 times of the basal values in the past 7 days, or decrease in the urinary output to < 0.5 mL/kg/h during 6 h, categorizing the episodes in three stages in relation to the severity of the renal damage (KDIGO 1, 2, or 3)[3].

Despite these barriers to diagnosis, it has been estimated that AKI occurs in 13.3 million people each year worldwide, 85% of whom live in countries with medium or low income, and the disease contributes to approximately 1.7 million deaths yearly. In a recently published meta-analysis that included 700 million hospitalized patients, 21% were found to have suffered from an AKI episode[5-7]. It is important to consider that AKI incidence is substantially higher in critically ill patients on the intensive care unit, i.e., 30-70%. In a study that included 49 million patients, it was observed that AKI occurred in one of five adults and one of every three hospitalized children[5,8]. Similarly, AKI etiology may vary depending on geographic region and socioeconomic conditions[5,9], but the most frequent causes of AKI are associated with generalized or localized ischemic damage due to surgeries, sepsis, trauma, infections, dehydration, and toxic drug damage[4]. In particular, several widely used agents, such as radiocontrast media or nonsteroidal anti-inflammatory drugs, can cause direct renal tissue damage, ischemic injury, or both.

Vascular endothelium in the AKI

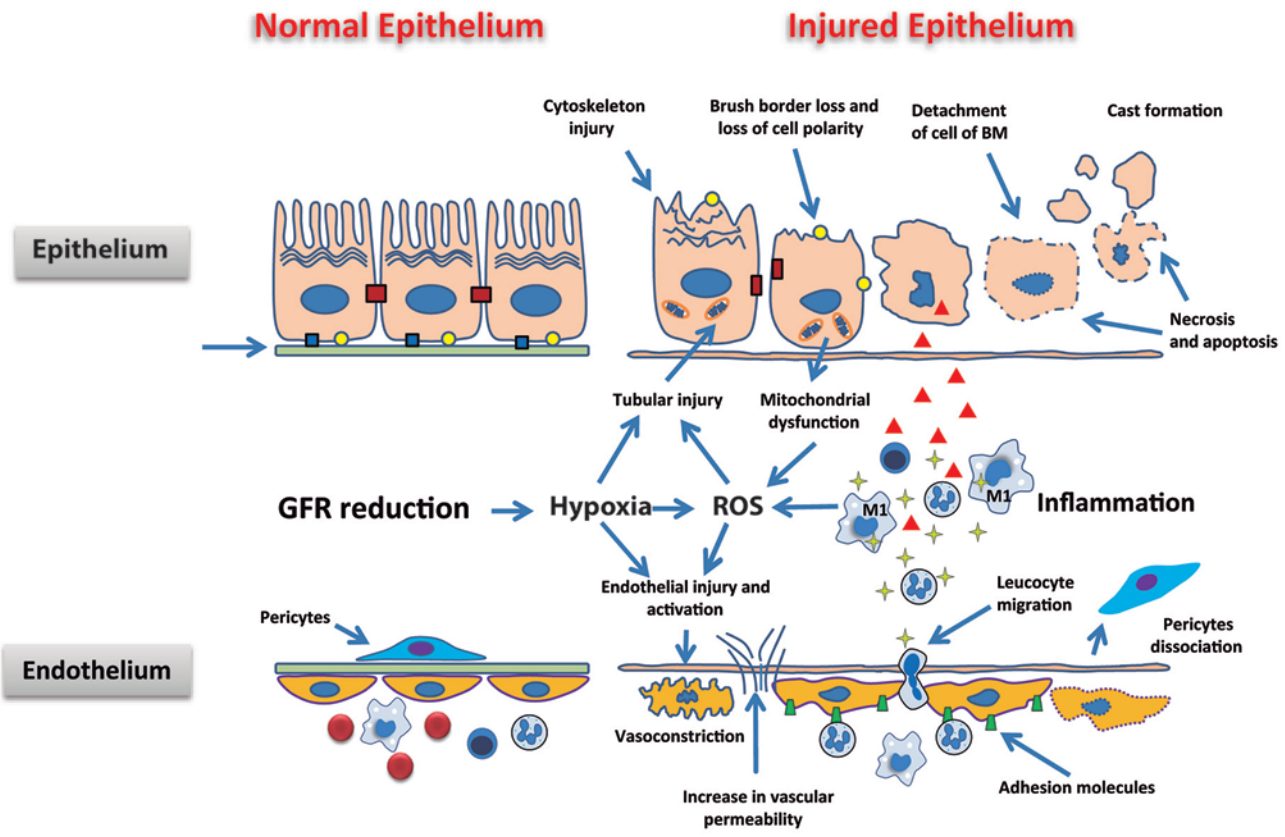
The kidney has one of the most abundant populations of endothelial cells compared with other organs[10,11]. The energy demand in this organ is high, and the partial pressure of oxygen is relatively low with fluctuating values between 40 and 60 mmHg in the cortex and 10 and 20 mmHg in the renal medulla[12]. Therefore, the vascular architecture is highly susceptible to blood perfusion and oxygenation[4,13]. Endothelial cells physiologically contribute to the maintenance of vascular tone, regulation of blood flow, and vascular permeability[14]. Vascular endothelial growth factor (VEGF) is required for the maintenance of the peritubular capillaries' homeostasis. VEGF is expressed in podocytes, proximal tubule, and thick ascending loop, while the VEGF receptors 1 and 2 are located in endothelial cells, and peritubular and glomerular capillaries[15,16]. AKI is accompanied by endothelium cell damage, which is characterized by the alteration of the actin cytoskeleton, causing the detachment of endothelial monolayer cells and affecting the tight intercellular junctions which, in turn, increase vascular permeability and the production of edema. Microvascular damage induces endothelial activation together with the expression of cell surface markers, such as intercellular adhesion molecules, which promote adhesion and recruitment of leukocytes and platelets[4]. The arterioles, particularly in the post-ischemic area, undergo intense vasoconstriction in response to an increase in tissue concentrations of endothelin, angiotensin II, thromboxane A2, prostaglandin H2, leukotrienes C4 and D4, and adenosine (Fig. 1). In addition, vasodilatation is limited in response to decreased acetylcholine, bradykinin, nitric oxide, and other vasodilator molecules[17]. The imbalance in the vasoactive release contributes to the decrease in renal blood flow and the maintenance of renal hypoperfusion after several hours.

Tubular epithelium in AKI

Once the hypoxic state occurs, tubular epithelial cells are unable to maintain adequate levels of adenosine triphosphate (ATP); therefore, they suffer damage and death, primarily by necrosis and apoptosis[17-19].

Figure 1. Integration of the mechanisms involved in acute kidney injury.

▲ Pro-inflammatory factors produced by the epithelium: tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, CXCL8, MCP-1, CCL5, and ENA 78.
✢ Pro-inflammatory factors produced by inflammatory cells: TNF-α, IL-1, CXCL8, MCP-1, and eicosanoids.
Endothelial adhesion molecules: intercellular adhesion molecules, P and E selectins.
Tight junctions.
Adhesion molecules (β-integrin).
Na+/K+-ATPase. M1: type 1 macrophages.



The proximal tubular epithelium is particularly more sensitive to hypoxic states than the rest of the tubular segments because it has a higher energy metabolic demand and a limited capacity for anaerobic glycolysis. It is well-known that the cytoskeleton has an integral role in cell function and structure through maintaining polarity, endocytosis, signal transduction, motility, organelle movement, exocytosis, cell division, and cell-matrix adhesion. Therefore, the damage to the tubular cytoskeleton has diverse effects on cellular function[14]. The ATP reduction also leads to the loss of the brush border of the proximal tubule, change in cell polarity, and alteration in the location of adhesion molecules and membrane proteins such as the Na^+K^+ ATPase pump and β-integrins. The relocation of the β-integrins and the lack of adhesion of the epithelial cells results in the exfoliation of these cells into the tubular lumen. The cellular debris combined with the Tamm-Horsfall protein and fibronectin promotes the distinctive cast formation in this disease, which may obstruct the tubules and later increase the intratubular pressure (Fig. 1)[17].

Inflammatory process in AKI

During AKI, an inflammatory cascade is initiated, where chemokines are the main mediators of inflammation, promoting the expression of adhesion molecules, and the activation and infiltration of leukocytes[20]. This inflammatory response involves cells of

the immune system such as neutrophils, monocytes/macrophages, dendritic cells, and natural killer lymphocytes[21,22]. Initially, the inflammatory process is characterized by the marginalization of the leukocytes to the activated vascular endothelium. Subsequently, there is a transmigration of the leukocytes to the inflammatory site[14]. Neutrophils and monocytes regulate the inflammatory process in the acute phase within the first 24 h[4]. The renal tubular epithelium also contributes to the exacerbation of the inflammatory process, since it synthesizes proinflammatory and chemoattractant molecules (Fig. 1). Several studies have shown that the prevention of the inflammatory process through the inhibition of neutrophils and monocytes/macrophages or by blocking endothelial cell-leukocyte interactions has a renoprotective effect[23,24]. T-lymphocytes are also involved in the development and maintenance of AKI. Accordingly, nude mice that are deficient in T-cells are protected from ischemia/reperfusion injury. Further studies, however, are warranted to elucidate in greater detail the participation and interaction of inflammatory cells with the resident neighboring immune cells[22].

Oxidative stress in AKI

Oxidative stress is also involved in the pathophysiology of both AKI and CKD[25-27], since it can affect renal hemodynamics by reducing the vasodilatory capacity of nitric oxide or by injuring the endothelial cells. Likewise, oxidative stress can also induce tubular epithelial damage by promoting cell death by apoptosis or necrosis[26]. The superoxide anion is the primary reactive oxygen species (ROS) that participates in injuring the kidney. There are also antioxidants that serve to protect the cellular integrity induced by ROS[25,26]. It is widely known that during renal injury, the intracellular antioxidants are reduced contributing to exacerbate the renal injury[25]. Particularly, the proximal tubular cells have abundant mitochondria; therefore, these cells are highly vulnerable to damage by the oxidative stress generated by hypoxia[28]. This organelle normally produces small amounts of ROS[29]. Under pathological conditions, the decoupling of oxidative phosphorylation and the loss to the integrity of the mitochondrial membrane induce an excessive amount of ROS coming from the respiratory chain, particularly complex I and III (Fig. 1). Mitochondrial dysregulation is also characterized by a decrease in cellular respiration and by a lower production of ATP as well as by the release of proapoptotic factors[25] Another frequent source of ROS in AKI corresponds to the infiltration of inflammatory cells, primarily neutrophils, and macrophages that, in addition to releasing a large number of pro-inflammatory cytokines, suffer the so-called respiratory burst, generating free radicals (Fig. 1)[26,27,30].

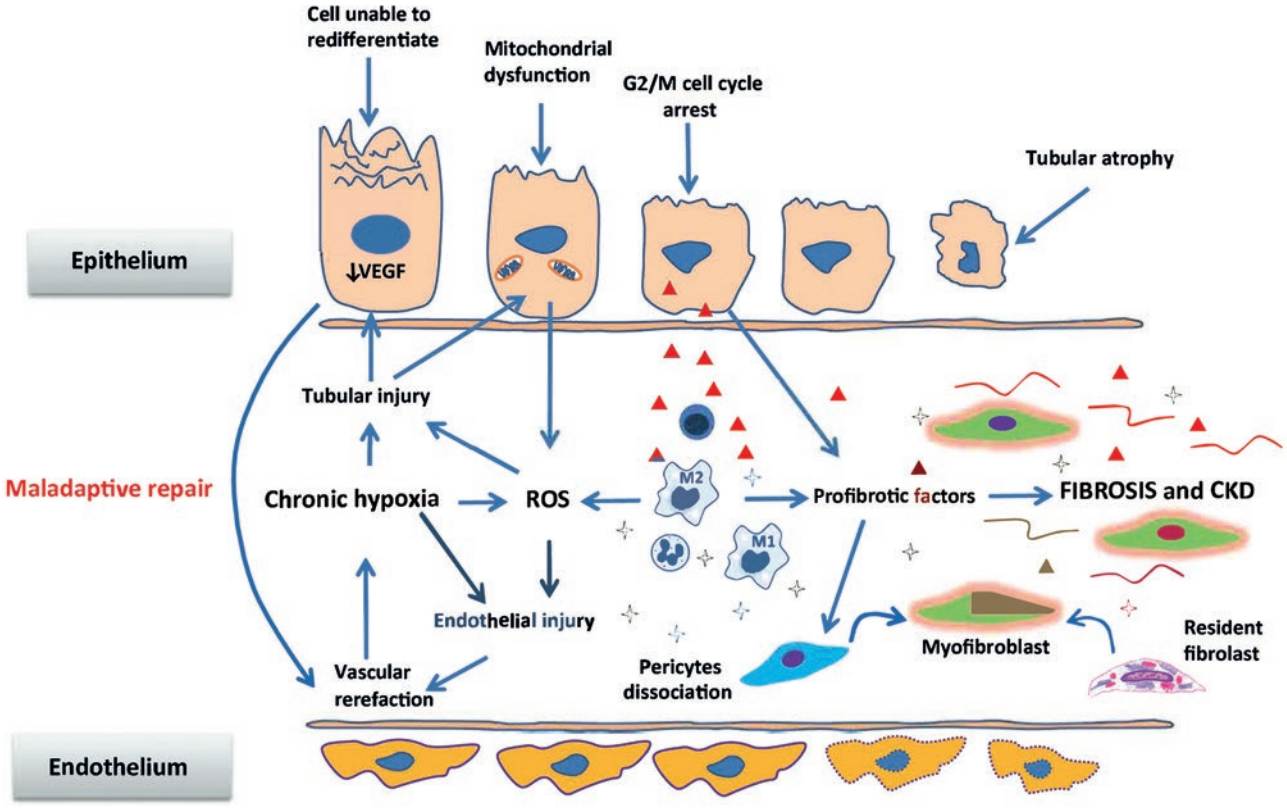
MECHANISMS INVOLVED IN THE TRANSITION OF AKI TO CKD

Several years ago, it was thought that patients who survived an episode of AKI and who had a recovery of renal function would not have long-term consequences[31]. However, in recent years, this concept has changed based on several experimental and epidemiological studies demonstrating that AKI is a risk factor, leading to progressive kidney disease[7,32-44]. In a recent meta-analysis that included 13 previously reported studies in patients who survived an AKI episode, the incidence of CKD and ESRD was 25.8% and 8.6%, respectively[34,35]. In addition, it has been reported that patients with greater AKI severity have a higher risk of a more rapid progression to CKD[36-38]. In older adults, the risk of ESRD after an AKI episode increases from 2 to 13 times[45]. However, in another study carried out in 126 children who presented with AKI without any other condition, 10% developed CKD in a period between 1 and 3 years[46].

The AKI to CKD transition has attracted the attention of several researchers, including those in our group, who have attempted to elucidate the mechanisms responsible for this transition. After an AKI episode, a complete repair of the function and renal structure, known as an adaptive response, would be expected; however, in most cases, this repair does not occur, since the repair seems to be incomplete or defective, known as a maladaptive response[4,47-49]. The working group of the 13th conference of the acute dialysis quality initiative has defined adaptive repair as the resolution of renal structure and function without long-term sequelae in a period of 90 days. Conversely, maladaptive repair was defined as a process that results from structural damage, such as renal fibrosis, and with consequent progressive reduction of renal function[49].

Figure 2. Integration of the mechanisms involved in the acute kidney injury to chronic kidney disease transition.

▲ Profibrotic factors produced by the epithelium: transforming growth factor (TGF)-β1 and connective tissue growth factor.
+ Profibrotic factors produced by inflammatory cells: TGF-β, platelet-derived growth factor-B, and fibroblast growth factor-2.
Extracellular matrix: fibronectin and collagen. M2: type 2 macrophages.



Several studies have shown that one hallmark of maladaptive repair is the persistence of the inflammatory process, proliferation of fibroblasts, and excessive deposition of extracellular matrix[43,44,50-56]. Therefore, the understanding of the mechanisms involved in the AKI to CKD transition will undoubtedly have an impact on the subsequent management of patients who suffered AKI.

Tubular epithelium in the transition of AKI to CKD

The renal tubular epithelium plays a central role in the fibrotic response that leads to progressive CKD[49,57-59]. The mechanism by which tubular cells promote renal fibrosis is complex; however, it has been described as a maladaptive repair because the epithelial cells lose the ability to redifferentiate and recover their normal structure; therefore, there is a pathological arrest in the G2/M phase of the cell cycle (Fig. 2)[54]. These abnormal epithelial cells have an intense signaling activity and express cytokines and profibrotic peptides that promote interstitial infiltration with inflammatory cells and the proliferation of fibroblasts[54,57,60]. The arrested cells in G2/M synthesize profibrotic factors: transforming growth factor (TGF)-β1 and connective tissue growth factor (CTGF)[49,54]. The specific and isolated lesion of the proximal tubule is sufficient to induce the activation of the inflammatory response, vascular rarefaction, and renal fibrosis[60,61].

Vasculature in the AKI to CKD transition

Basile et al.[62], Babickova et al.[63], and Hörbelt et al.[64] have shown that capillary density is reduced up to 45%, 4 weeks after inducing AKI in murine models. This finding indicates that unlike the tubular

epithelium, the vascular epithelium has less regeneration potential[10]. The absence of vascular repair is due to the reduction in the expression of VEGF[12,60,63]. In fact, it has been shown that administration of VEGF after ischemia preserves capillary density in the rat[65]. Vascular rarefaction may be a key element in the development of fibrosis, since it maintains renal tissue in a chronic hypoxic state, which initiates the activation of hypoxia-induced signaling pathways. Accordingly, the reduction of renal capillary density correlates with the severity of fibrosis[62].

Chronic renal hypoxia has been considered a therapeutic target for the AKI to CKD transition[12,66.] Hypoxia also has other deleterious effects, since it is the cause of apoptosis in renal epithelial cells and may activate local fibroblasts that contribute to fibrogenesis[62]. Renal fibrosis aggravates hypoxia, further reducing the efficiency of oxygen diffusion by increasing the distance between capillaries and tubules[59]. In addition, *in vitro* studies have linked hypoxia to the inflammatory process because it induces leukocyte adhesion to the endothelium through the activation of β2 integrin[67]. It is not entirely clear how vascular rarefaction and chronic hypoxia persist because hypoxia-inducible factor (HIF) must be activated and initiates the induction of multiple angiogenic factors to stimulate a vascular compensatory response; however, this mechanism is not well activated and almost always is not sufficient to avoid vascular rarefaction[15].

Origin of cells that induce fibrosis (myofibroblasts)

The origin of myofibroblasts is under debate and has stimulated intense research in this field[13,49,53,60,62,68]. Several studies have reported that pericytes are the primary cells that contribute to the accumulation of myofibroblasts through the transdifferentiation of pericyte-myofibroblast[69-72]. Pericytes are specialized cells that are attached to endothelial cells and maintain vascular stability and integrity. The loss of pericytes of the vascular endothelium together with its participation in renal fibrosis causes instability in the capillaries, thereby contributing to vascular rarefaction[13]. It has also been reported that this process is accompanied by the upregulation of platelet-derived growth factor receptor (PDGFR)-β and PDGFR-α, while pharmacological blockade of these receptors prevents the dissociation of pericytes[69]. The vascular stability is also reduced after renal damage by alterations in the regulation of the tissue inhibitor of metalloproteinases 3 and disintegrin, and metalloproteinase with thrombospondin motifs 1, which are genes that regulate proteolysis and angiogenesis in the pericyte[73,74]. Other cells that could be involved in the origin of myofibroblasts are resident fibroblasts, cells derived from the bone marrow, endothelial cells, and erythropoietin-producing cells[75]. It has been suggested that myofibroblasts may also have their origin derived from the damaged tubular epithelium, due to the process of epithelial-mesenchymal transdifferentiation; however, several studies question this statement[70,75].

Inflammatory process in the AKI to CKD transition

Macrophages, in particular, play a central role in both the injured cells and in the repair of the affected tissue[4]. The sustained infiltration of macrophages can induce fibrosis and progression to CKD by generating profibrotic cytokines including TGF-β, PDGF-B, and fibroblast growth factor 2, which promote proliferation and survival of myofibroblasts. After AKI, the presence of two subtypes of macrophages that may differentiate under the influence of the local microenvironment has been demonstrated[22,76]. Type 1 (M1) macrophages (induced by interferon and lipopolysaccharides) migrate immediately after renal injury and are responsible for the production of pro-inflammatory molecules, while macrophages Type 2 (M2) (stimulated by interleukin [IL]-4 and IL-13) arise in the recovery phase of AKI and synthesize factors that help in the proliferation of tubular cells and the repair of renal damage[76].

Sexual dimorphism in the AKI to CKD transition

A rarely investigated aspect in the pathophysiological course, clinical presentation, and prognosis of kidney disease is the marked differences that exist between men and women. Several studies in different renal pathologies have shown that men are more susceptible than women[77]; however, the mechanisms have not been fully elucidated. Our laboratory has been interested in this phenomenon, particularly in what occurs in the AKI to CKD transition, considering that by deepening the mechanisms of renoprotection in females or susceptibility in males, new therapeutic

targets might be identified. Female and male rats underwent a period of bilateral renal ischemia for 45 min and were evaluated after 24 h, 1, 2, 3, and 4 months after ischemia. In addition, oophorectomized rats were also used. As we previously reported[43,55,78], male rats experienced the AKI to CKD transition 4 months after renal ischemia, unlike female rats that did not have this transition. The mechanisms of renoprotection in female rats were associated to an increase in antioxidant enzymes and, therefore, less oxidative damage. Moreover, it was observed that the female rats had a significant increase in mRNA levels of eNOS, TGF-β, and HIF-1α. A particularly interesting finding was the fact that female oophorectomized rats behaved similarly to male rats; in other words, this group developed CKD[44]. These results strongly suggest the participation of sex hormones in the transition from AKI to CKD.

In summary, the growing evidence in the close relationship and dependence between AKI and CKD has stimulated the interest of several research groups that have made important contributions to the body of knowledge regarding the mechanisms that bridge these two pathologies. However, given the great complexity, the different cell types and the diversity of factors involved, there are still many questions to answer.

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