Acute Kidney Injury (AKI)

Subjects: Others

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Acute kidney injury (AKI) is characterized by an acute loss of renal function. In clinical practice, AKI is defined by an elevation of creatinine plasma concentration above ≥0.3 mg/dL in the first 48 h, an urine volume below 0.5 mL/kg/h for 6 h, or an 1.5 fold increase in serum creatinine as compared with the baseline values.

Keywords: toll-like receptors ; inflammation ; acute kidney injury

1. Introduction

Reduction in urinary volume and urinary solute excretion leads to accumulation of waste products in the body as well as dysregulation of blood pH and osmolarity, that may result lethal for the patient. Depending on the intensity of AKI, the use of dialysis for patient survival may be necessary.

In the last years, the incidence of AKI has increased considerably as a consequence of the high prevalence of AKI-associated comorbidities, such as aging, chronic kidney disease (CKD), diabetes and hypertension, among others [1]. In fact, it has been estimated that around 13.3 million people/year develop AKI [2].

Many people fully recover renal function after the AKI episode, however there are patients that progress to CKD, suggesting adverse chronic outcomes [3]. Indeed, AKI patients have a higher risk to develop CKD than healthy individuals. Moreover, AKI is associated with high frequency of cardiovascular events and both early and long-term mortality [4]. Despite these adverse outcomes, there are no specific treatments to reduce chronic renal damage after AKI. Therefore, it is necessary a better comprehension of the physiopathology associated to this syndrome to identify novel therapeutic approaches.

2. Pathophysiology of AKI

The etiology and pathophysiology of AKI are complex and multifactorial. AKI can be classified into three different types: pre-renal, intrinsic and post-renal. Pre-renal AKI is associated to a decreased renal blood flow by hypovolemia, impaired cardiac function, systemic vasodilation or increased vascular resistance, thus leading to a reduced glomerular filtration rate (GFR). Intrinsic AKI is related to direct injury or nephrotoxicity of parenchymal renal cells (glomeruli, tubules, interstitium and endothelial cells). Post-renal AKI is mainly related to a reduction in GFR as consequence of increased intra-tubular pressure by obstruction of urinary tract [5].

The underlying pathophysiological mechanisms in AKI include hemodynamic changes, direct tubular toxicity (mainly in proximal tubular cells), obstruction and dysfunction of microvascular vessels, congestion of tubular lumen, and renal inflammation [6]. These pathogenic mechanisms may co-exist in AKI-patients, thus complicating diagnosis and treatment.

AKI depends on the duration and severity of the insult [7]. When acute renal damage occurs, there is a first phase of tubular death, followed by a phase of cell regeneration and recovery of the renal function. Massive tubular cell death results from different causes, such as toxic insults, sepsis, oxidative stress, or ischemia, among others [8]. If the cause of kidney damage is prolonged over time, it can trigger more severe tubular cell death. During this process, tubular cells release chemokines, cytokines and other inflammatory stimuli that promote leucocyte infiltration in the kidney [9][10]. Inflammation is important for the regeneration and replacement of necrotic cells during AKI [11][12]. However, exacerbated or unresolved inflammation triggers the activation of fibrosis, a phenomenon that may be involved in progression to CKD after AKI [6].

3. Biomarkers in AKI

In the current clinical practice, AKI diagnosis is mostly based in determination of serum creatinine concentration [13]. However, the levels of this nitrogen-containing compound only increase when kidney injury is well stablished, restricting the possibility to detect early phases of AKI [14]. In addition, many factors influence serum creatinine concentration e.g., age, gender, diet, muscle mass, and hydration status), limiting its utility as an AKI biomarker. For these reasons, there is a great interest in the search of new AKI biomarkers for early detection, differential diagnosis and prognosis [15][16]. In this context, the most promising AKI biomarkers are listed in Table 1. These novel biomarkers are related with pathological processes involved in AKI development, such as inflammation, oxidative stress and renal cells death [17][18]. Furthermore, current studies support the potential value of circulating and urinary miRNAs as novel AKI biomarkers e.g., miR-21, miR-30a-e and miR-494, among others [16][19][20].

Table 1. AKI biomarkers.

Biomarker	Function	Origin	Samples
Cystatin C	Extracellular cysteine protease inhibitor	All nuclear cells	Serum
NGAL	Limits bacterial growth by sequestering iron-containing siderophores	Neutrophils	Serum/Urine
IGFBP7	Main regulator of IGFs availability in cells	Renal and inflammatory cells	Urine
TIMP2	Peptidase involved in MMP inhibition and ECM degradation		
CCL14	Pro-inflammatory chemokine		
IL-18	Pro-inflammatory cytokine		
KIM-1	Phosphatidylserine receptor that recognizes apoptotic cells and oxidized lipoproteins	Tubular cells	
NAG	Hydrolytic lysosomal enzyme		
NHE3	Sodium–hydrogen exchanger in apical side of the epithelial cells		
α/π-GST	Phase II enzyme involved in cellular detoxification		
ALAP	Enzymes involved in tubular damage		
AP			
γGT			
L-FABP	Cytoplasmic proteins involved in binding, transport and metabolism of LCFAs		

Abbreviations: CCL14: Chemokine (C-C motif) ligand 14; ECM: Extracellular matrix; GST: Glutathione-S-transferase; IGF: Insulin growth factor; IGFBP7: Insulin-like growth factor-binding protein 7; IL-18: Interleukin-18; KIM-1: Kidney injury molecule-1; LCFA: Long-chain fatty acid; L-FABP: liver-type fatty acid binding protein; NAG: N-acetyl-β-D-glucosaminidase; NHE3: Sodium-hydrogen exchanger isoform 3; NGAL: Neutrophil gelatinase-associated lipocalin; MMP: Metalloproteinase; TIMP2: Tissue inhibitor of metalloproteinases-2.

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