Acute Kidney Injury

Subjects: Others

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Acute kidney injury is a common complication in critically ill patients with sepsis and/or septic shock. Further, some essential antimicrobial treatment drugs are themselves nephrotoxic. For this reason, timely diagnosis and adequate therapeutic management are paramount. Of potential acute kidney injury (AKI) biomarkers, non-protein-coding RNAs are a subject of ongoing research.

: acute kidney injury gentamicin sepsis miRNA

1. Introduction

Acute kidney injury (AKI) is a common and mostly severe clinical syndrome complicating a number of critical illnesses. It has a highly negative impact on patient morbidity, mortality and clinical outcome. The diagnosis is generally based on evaluation of: (1) increase in serum creatinine and/or (2) decrease in urinary output. According to the KDIGO (Kidney Disease Improving Global Outcomes) classification of 2012, the severity of urinary output deterioration to terminal stages and presentation of an anuria and serum creatinine increase to 353.6 µmol/L is the most serious stage 3 [1]. Further, in 2017, new forms of acute renal impairment were described with AKI lasting at least 7 days after insult and acute kidney disease (AKD) lasting up to 90 days. Renal impairment and serum creatinine levels that had not returned to baseline levels by 90 days resulted in the need for renal replacement therapy (RRT) and/or progression to chronic kidney disease (CKD) [2]. Timely AKI diagnosis, especially in critically ill patients, would enable clinicians to better initiate preventive measures to avoid the need for RRT and obviate the risk of CKD. A number of promising new biomarkers may be able to predict the development or worsening of AKI in intensive care. The most highlighted of these in recent years are noncoding microRNAs in these circumstances. This review focuses on the pathophysiology and potential biomarkers in the detection of AKI after nephrotoxic drugs and/or septic insults with emphasis on specific microRNAs.

2. Epidemiology of Acute Kidney Injury

Acute kidney injury is a relatively frequent complication in critically ill patients in ICUs, especially in those with sepsis. The incidence of AKI in these circumstances, predominantly in situations with presentation of septic shock, may be as high as 47.5% and the overall mortality in critically ill patients with AKI may be more than 60% [3]. According to recent results of a multicenter Chinese study of patients hospitalized in ICUs, the incidence of AKI was 51%, with the majority occurring on the 4th day after admission [4]. A number of factors can contribute to AKI and progression to renal failure, including cardiovascular and hepatic disorders, malignancies, hypovolemia,

intoxication, drug nephrotoxicity, anemia and surgical and vascular interventions. Further, many such patients need nephrotoxic iodine contrast drugs for CT scans and other radiological examinations. Therefore, the AKI is often a consequence of multiple factors.

3. Pathophysiology of Sepsis-Induced Acute Kidney Injury

Sepsis is generally characterized as a life-threatening condition induced by any type of infection (e.g., bacterial, viral, mycotic) and the dysregulated response of the host organism, with subsequent organ and tissue dysfunction or failure. The diagnosis has recently been redefined according to the SEPSIS-3 consensus (The Third International Consensus Definitions for Sepsis and Septic Shock) as an increase in the SOFA (Sequential Organ Failure Assessment) score of 2 points or more. For earlier clinical decision-making, the Quick SOFA (qSOFA) criteria can be used as evaluation of: altered mental status, a respiratory rate of 22/min or greater and a systolic blood pressure of 100 mmHg or less [5]. The pathophysiology of sepsis-induced AKI appears to be multifactorial, including, among others, deleterious inflammatory cascade [6]. Underlying explanations of septic AKI development include: (1) alteration of the renal macro- and microcirculation, with subsequent endothelial dysfunction, (2) damage of renal tubular epithelial cells, (3) a change in cellular metabolic pathways and energy consumption, (4) mitochondrial injury, (5) reactive oxygen species (ROS) production and (6) cycle cell arrest [7]. However, the exact mechanism of septic AKI is still unclear. Increase in inflammatory cytokine production and activation of leukocyte activity in the context of a dysregulated immunological and inflammatory response can lead to production of intravascular microthrombi and also reduce intrarenal blood flow and oxygen delivery [8]. Regulation of the immune and adaptive immunity response in renal tubular cells occurs due to activation of the Toll-like receptor (TLRs) family in the cell membrane. There are more than 13 members of this family and they are usually activated by endotoxins. They recognize pathogen-activated molecular patterns (PAMPs) and damage-associated pathogens (DAMPs) with the promotion of leukocyte and intrinsic renal cell activation. Renal tubular cells express TLR-1, -2, -3, -4 and -6, which can be substantially involved in the pathophysiology of tubular cell damage [9][10]. The most important receptor in septic AKI pathophysiology appears to be TLR-4, that can bind the endotoxin lipopolysaccharide (LPS), leading to activation of a number of intracellular signaling pathways via the nuclear-κB (NF-κB) transcription factor. NF-κB response to endotoxin stress leads to activation and release of the inflammatory cytokines TNFα, IL-1, IL-6 and IL-8 [11]. The activation of NF-κB depends on the phosphorylation and degradation of inhibitory κB proteins, triggered by specific kinases [9]. The basic explanation of the pathophysiological pathway in septic AKI development via activation of TLR-4 receptors in proximal tubular cells very likely lies in dysregulation of tubular integrity, with induction of tight junction disruption. This process may contribute to subsequent oliguria and decrease in renal function [12]. A recent animal study (Nakano et al., 2020), where conditional knockout of TLR-4 in proximal tubular cells reduced LPS-induced paracellular leakage of filtrate into the interstitium via TLR-4 showed that the interstitial leakage and accumulation of extracellular fluids lead to anuria and diminished the efficacy of volume resuscitation, which is frequently used in septic AKI to restore renal function [13].

4. Biomarkers of Sepsis-Induced Acute Kidney Injury

Many potential biomarkers have been studied in recent years in the context of sepsis and septic AKI. These can be divided into: (1) standard biomarkers, (2) additional urinary and/or serum biomarkers, (3) metabolomics, (4) other experimental proteomics and (5) microRNAs (miRNAs). Generally, AKI is diagnosed by the standard use of serum creatinine concentration and urinary output, as mentioned, with additional evaluation of serum concentration of urea. In addition, we can include Neutrophile gelatinase-associated lipocalin (NGAL), Cystatin C, Kidney Injury Molecule -1 (KIM-1), Interleukin 18 (IL-18), urinary Insulin-like growth factor-binding protein-7 (IGFBP-7), urinary tissue inhibitor of metalloproteinase 2 (TIMP-2), calprotectin, urine angiotensinogen and liver fatty acid binding protein [14]. In clinical practice, especially in patients with AKI in ICUs, it is very useful to have a biomarker capable of predicting the need for RRT initiation, renal recovery or transition to chronic nephropathy. According to a meta-analysis of 63 studies comprising 15,928 critically ill patients, the best evidence was for blood NGAL and Cystatin C followed by urinary TIMP-2 and IGFBP-7 [15]. However, decision-making in the case of RRT initiation is based on a number of clinical and laboratory findings, not only biomarkers, and none of these is specific to any particular type of AKI [16]. The major limitation of biomarkers in the AKI condition lies in comparing biomarkers to serum creatinine and diuresis, the basic diagnostic tools for AKI [17].

In recent experimental animal models of septic AKI, some potential novel metabolomic biomarkers have been identified using nuclear magnetic resonance spectroscopy on urine, renal tissue and in serum. Alterations in the concentration of several metabolites have been found e.g., lactate, *N*-acetylglutamine, alanine, pyruvate, myoinositol, glutamine, valine, glucose, ascorbic acid, aminoadipic acid, *N*-acetylaspartate and betaine and these correlate with serum creatinine and NGAL [18]. Further, many heat shock proteins (HSP) families and their bioactivity are described in various kidney diseases. In ischemic, toxic or other forms of AKI, the following have been found expressed in several renal cell types (podocytes, mesangial cells, tubular cells, fibroblasts, endothelial cells, macrophages): HSP27, HSP70, HSP60, HSP47, HSP90 and HSP32 [19]. Their main role in renal cytoprotection is still under investigation. However, many of them can block the apoptotic death pathway, oxidative stress, cell proliferation and differentiation, mediation of the inflammatory response and inhibit fibrogenesis [19]. A study of 56 critically ill patients, where 17 of them suffered from AKI, revealed that urinary HSP72 levels significantly increased in the period of three days before AKI and remained elevated during AKI diagnosis [20].

5. MiRNAs as Biomarkers of Septic Acute Kidney Injury

Research is currently focused on miRNAs as new potential biomarkers and/or therapeutic tools for many conditions including AKI. MiRNAs are small molecules (18–31 nucleotides) of noncoding RNAs, representing a large part of genetic information not translated from the DNA matrix into final protein production. The evidence of their abundance, developmentally regulated fashion and often subcellular localization points to their important biological role in many biochemical and pathophysiological processes and pathways on the cellular and molecular level [21]. Influence on post-transcriptional gene regulation, cell metabolism, cytokine production, cell differentiation and programmed cell death are only a small percentage of miRNAs' effects and their target genes. In the AKI condition, some act protectively and can become potential therapeutic targets but others can increase the toxic activity and renal damage. Anti-inflammatory and/or anti-apoptotic activity in AKI has been described for the following miRNAs:

miR-10a, *miR-21*, *miR-26a*, *miR-122*, *miR-126*, *miR-146a*, *miR-199a*, *miR-296* and *miR-494* [22]. Some miRNAs involved in the pathophysiological inflammatory process of sepsis based on endotoxin (LPS) activation of TLR4 in the signaling pathway of NF-κB activation, pro-inflammatory cytokine production (IL-6, IL-1β, TNFα) and subsequent neutrophil activation, damage of endothelial permeability and tissue injury are: *miR-146 a/b*, *miR-223*, *miR-155*, *miR-203*, *miR-15a*, *miR-16*, *miR-126*, *miR-199a* and *miR-9*. Each regulates positively or negatively a different part of the biochemical cascade to final cytokine production and tissue damage according to their target genes [23][24]. In the development of septic AKI, severe metabolic alterations of tubular epithelial cells may play a crucial role via *miR-21-3p* influence on the *AKT/CDK2-FOXO1* pathway, with induction of cycle cell arrest and apoptosis [25]. According to one human study (Ge et al., 2017), many other signaling pathways are involved in septic AKI development, including oxidative stress and mitochondrial dysfunction pathways (*HIF-1*, *PI3K-Akt*, *mTOR* and *TGFβ*). In septic, critically ill patients, significantly overexpressed *miR-4321* was observed, with the predicted oxidative-stress-associated target genes: *AKT1*, *MTOR*, *NOX5*, *IL17RA* and *IL26* [26]. The mitochondrion is assumed to be a key organelle in the development of septic acute kidney injury, and has major pathophysiological significance in ROS production and apoptosis [27]. In one hybrid human and experimental study including 50 patients with sepsis, an effect was found of *miR-106a* on caspase-3 activity, *BCl-2* expression and proinflammatory cytokine production after LPS stimulation [28]. The authors found an association between *miR-106a* and an aggravation of LPS-induced inflammation, and apoptosis in sepsis-induced AKI. A target gene for *miR-106a* was established as thrombospondin *THBS2*, which takes part in a number of processes such as regulation of cell motility, death and cytoskeleton formation [28].

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