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Narrative Review

The ischemic/nephrotoxic acute kidney injury and the use of renal biomarkers in clinical practice

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ABSTRACT

The term Acute Renal Failure (ARF) has been replaced by the term Acute Kidney Injury (AKI). AKI indicates an abrupt (within 24–48 h) decrease in Glomerular Filtraton Rate, due to renal damage, that causes fluid and metabolic waste retention and alteration of electrolyte and acid-base balance. The renal biomarkers of AKI are substances or processes that are indicators of normal or impaired function of the kidney. The most used renal biomarker is still serum creatinine that is inadequate for several reasons, one of which is its inability to differentiate between hemodynamic changes of renal function ("prerenal azotemia") from intrinsic renal failure or obstructive nephropathy. Cystatin C is no better in this respect. After the description of the pathophysiology of "prerenal azotemia" and of Acute Kidney Injury (AKI) due to ischemia or nephrotoxicity, the renal biomarkers are listed and described: urinary NAG, urinary and serum KIM-1, serum and urinary NGAL, urinary IL-18, urinary L-FABP, serum Midkine, urinary IGFBP7 and TIMP2, urinary α-GST and π-GST, urinary γGT and AP, urinary β_2M, urinary RBP, serum and urinary miRNA. All have been shown to appear much earlier than the rise of serum Creatinine. Some of them have been demonstrated to predict the clinical outcomes of AKI, such as the need for initiation of dialysis and mortality.

The term Acute Renal Failure (ARF) secondary to ischemic/nephrotoxic injury should no longer be used, but replaced by the term Acute Kidney Injury (AKI) indicating an abrupt (within 24–48 h) decrease in Glomerular Filtraton Rate (GFR) that causes fluid and metabolic waste retention and alteration of electrolyte and acid-base balance [1–3]. The word "injury" includes the entire range of renal impairment from small changes of serum creatinine (SCr) to the complete loss of renal function [3]. The term ARF is limited to patients with a decrease in GFR so severe to require renal replacement therapy [4].

1. Severities of AKI

Two groups of nephrologists have defined the different severities of AKI. According to the RIFLE (acronym of *"Risk of injury, Injury, Failure, Loss of function, and End-stage renal failure"*) classification [5] the increase in SCr over 7 days correlates with the severity of AKI. The lowest degree of severity of AKI was defined as risk: an increase of SCr 1.5 times the normal level with urine output <0.5 mL/Kg for 6 h; injury: an increase in SCr 2 times the normal level with urine output <0.5 mL/Kg for 12 h; failure: an increase in SCr 3 times the normal level with urine output <0.5 mL/Kg for 12 h or anuria for 12 h; loss: the complete loss of renal function for >4 weeks; end-stage kidney disease: the need for dialysis for >3 months [6]. The other group suggested the AKIN (acronym of *Acute Kidney Injury Network*) classification that eliminated the last 2 degrees of RIFLE, calling the first 3 degrees (*Risk, Injury and Failure*) stages I, II and III respectively and defining AKI as an increase in SCr over 48 h [1,3].

AKI has to be differentiated from "Prerenal azotemia".

1.1. Pathophysiology of "Prerenal azotemia" ("functional" renal failure)

The normal kidney has a peculiar property, called "renal autoregulation": it can face wide changes in renal perfusion pressure without modifying renal blood flow (RBF) and GFR. In any condition of hypovolemia, the renal perfusion pressure falls. Should it fall below the lower limit of the autoregulation (this occurs when blood pressure < 80 mmHg), RBF and glomerular capillary pressure will decrease causing a fall in GFR. Furthermore, hypovolemia may stimulate the adrenergic nervous system with a subsequent release of vasoconstricting hormones which cause renal vasoconstriction aggravating the renal hypoperfusion. Under such circumstances, the kidney is not damaged despite a rise in SCr [7].

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The same phenomenon is realized in cases of contraction of the "effective" circulating blood volume (relative fullness of the arterial tree, as determined by cardiac output, peripheral vascular resistances and total blood volume), as it occurs in congestive heart failure [8], in cirrhosis with ascites and in nephrotic syndrome [7–10].

"Prerenal azotemia" is the fall in GFR due to renal hypoperfusion caused by an ischemic insult, associated with an increase in SCr and retention of nitrogenous metabolic waste, as a consequence of a major hemorrhage or a severe ExtraCellular Volume (ECV) depletion, due to extrarenal losses of fluid (by vomiting and/or diarrhea, by gastric, enteric or biliary drainage, by enterostomy, by abuse of laxatives or loss through sweating) or to losses of fluid with urine (by glucose or salt-losing nephritis or by abuse of diuretics) or to losses in the "third-space" (by pancreatitis or intestinal obstruction). In the "functional" renal impairment the renal tubules are intact, not damaged, perfectly functioning; thus, the fractional excretion of sodium ($FE_{Na} = [U_{Na} \times P_{Cr}/P_{Na} \times U_{Cr}] \times 100$) is <1.0%, indicating that the tubules are reabsorbing avidly the tubular fluid with the aim to normalize the contracted ECV: the result is oliguria with concentrated urine and low urinary sodium (usually <20 mEq/L) and normal urinary sediment. This condition is usually reversed by adequate treatement. However, it is the most frequent cause of renal impairment in aged patients [7,11–13].

Clinical signs of salt depletion and ECV contraction will be postural hypotension associated with tachycardia and decrease in central venous pressure.

1.2. Pathophysiology of Acute Kidney Injury (AKI) due to ischemia or nephrotoxicity

AKI may represent an evolution of untreated "Prerenal azotemia" if renal damage occurs. However, even a severe salt depletion caused in normal subjects by diuretics plus low salt intake is not followed by AKI. Thus, some factor(s) is(are) associated with the salt depletion in causing "intrinsic" renal failure. Anyhow, in ischemic/nephrotoxic AKI the lesions occur primarily in the renal tubular epithelium [14–25]. Upon renal biopsy, the tubular lesions are, in fact, the first variable phenomenon in extension and severity, initially seen only under electron microscopy (degeneration of nuclei, swelling of mitochondria, distortion of the cristae), then visible also under light microscopy. But, before these microscopic changes become visible in the tubules, a loss of some enzymes and/or molecules takes place in the tubules, representing an early phenomenon; thus, the substances lost in the urine may be used as renal biomarkers.

Clinical signs of severe ischemic/nephrotoxic AKI include oliguria (secondary to the fall in GFR) until a complete anuria, hyponatremia (that may be due to water overload because of anuria), metabolic acidosis, hyperkalemia, hypocalcemia, hyperphosphatemia, anemia, frequently associated with nausea, vomiting leading to chronic dialysis requirement (ischemic/nephrotoxic ARF), sometimes gastrointestinal bleeding, enterocolitis, infection, that is usually the cause of death [26–28].

What is peculiar about ischemic/nephrotoxic AKI is the high urinary sodium concentration (>40 mEq/L) due to the reduced capacity of the renal tubular epithelium to reabsorb sodium, despite the frequent presence of salt depletion with hypovolemia. Thus, FE_{Na} is >2% in the absence of glucosuria or the use of diuretics.

1.3. The most used renal biomarkers: SCr and serum Cystatin C (Cys-C)

We may define the renal biomarkers of AKI substances or processes that are indicators of normal or impaired function of the kidney.

Most studies on AKI are still using SCr as indicator of kidney injury despite its poor sensitivity and specificity and poor accuracy of renal damage [4,29,30]. SCr is not adequate for an early identification of GFR reduction: it does not allow differentiation between hemodynamically mediated changes in renal function ("prerenal azotemia") and intrinsic renal failure or obstructive nephropathy; SCr may not rise until a marked decrease of GFR has occurred, thus, it takes several hours or days for SCr to reach a new *steady state*; SCr reflects the real value of GFR under *steady state* conditions, but not when renal function is decreasing; important fluctuations occurs, during the day in creatinine production from the creatine of muscles, even in normal subjects; SCr varies with age, gender, race and weight. The last problem is overcome by using the estimated glomerular filtration rate (eGFR), i.e. the Creatinine Clearance (CrCl) calculated either by the MDRD (Modification of Diet in Renal Disease) formula or by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation or by the Cockcroft-Gault formula. Undoubtedly, in our opinion both, the MDRD and the CKD-EPI formulas, are more accurate than the Cockcroft-Gault formula [31–33]. However, we prefer using the latter in clinical practice, at the bed side, when we do not need an extremely precise value of eGFR, because it is easy to memorize and simple to calculate without the need of a calculator: (140 − number years of age) × Kg body weight/72/mg/dL of serum creatinine; in females the result has to be multiplied by 0.85. Obviously, in the case of a medical research setting, either MDRD or CKD-EPI would be preferred. Creatinine is not only filtered by the glomerulus, but also secreted by the renal tubule and the secreted component may vary when the kidney is damaged and when other drugs (cimetidine, trimethoprim, and salicylates) modify its tubular secretion [34,35]. In this respect, Cystatin C is better than creatinine.

Cystatin C is another biomarker of GFR produced at a constant rate by all nucleated cells, is not bound to plasma proteins and, therefore, is freely filtered by the glomerulus and reabsorbed by the proximal tubule where it is degraded by megalin [36]. It is not secreted by renal tubules and does not vary with gender, race, weight, changes of muscle mass, and nutrition. The half-life of Cystatin C (1.5 h) is three times shorter than that of Creatinine; thus, its serum concentration will rise more rapidly than SCr when GFR decreases [37–41]. But marked albuminuria decreases tubular reabsorption of Cystatin C because albumin is also reabsorbed by megalin-facilitated endocytosis thereby competing with its tubular reabsorption. This makes Cystatin C an unreliable marker of GFR when proteinuria is present [35,36,39,42,43].

1.4. The renal biomarkers of ischemic/toxic AKI

We need new biomarkers for an earlier diagnosis of ischemic/nephrotoxic AKI.

A good biomarker (a) should theoretically be easy and simple to be measured; (b) should have earlier detectability than the rise of SCr, in order to allow the diagnosis of AKI as early as possible; (c) should allow the distinction of AKI from "prerenal azotemia" and from chronic kidney disease; (d) should identify type and location of the cause of AKI; (e) should indicate the severity of incoming AKI and some estimate as to the timing of its onset; (f) should allow the prediction of the patient's outcome (recovery, dialysis and mortality) [35,43–45]; (g) should allow monitoring of pharmacological responses to therapy. [46,47]

2. NAG

N-acetyl-β-D-glucosaminidase (NAG) is an enzyme produced by the lysosomes of the renal proximal tubular cells. It can be found in the urine of normal subjects in very small amounts. Because of its high molecular weight, it cannot be filtered by glomeruli; thus, its increase in the urine derives from tubular damage [48,49]. It occurs in AKI between 12 h and 4 days before the rise in SCr. Westhuyzen et al. [50] have carried out a study on 26 consecutive patients admitted to the Intensive-Care Unit (ICU); 4 patients had ARF (the authors do not use the term AKI as yet) (ARF group). At the time of admission the urine of the control group (n. 22) had a low concentration of NAG (15.1 U/L) that remained about the same after 12 and 24 h. The urine of the ARF group (n. 4) had very high concentrations of NAG (20.7 U/L) on