Review

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Review

Biomarkers in Contrast-Induced Acute Kidney Injury: Towards a New Perspective

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Abstract: Contrast-Induced Acute Kidney Injury (CI-AKI) remains a frequent iatrogenic condition since radiological procedures using intra-vascular iodinated contrast media (CM) are being widely administered for diagnostic and therapeutic purposes. Despite the improvement of the medical healthcare system worldwide, CI-AKI is still associated with direct short-term and indirect long-term outcomes including increased morbidity and mortality, specially, in patients underlying pre-existing renal function impairment, cardiovascular disease or diabetes that could rapidly progress into Chronic Kidney Disease. Although the RIFLE (Risk, Injury, Failure, Loss, End-Stage Kidney Disease), AKIN (Acute Kidney Injury Network) and KDIGO (Kidney Disease Improving Global Outcomes) clinical criteria and recommendation guidelines are based on traditional "gold standard" biomarkers known as serum creatinine, glomerular filtration rate and urinary output, new reliable serum and urinary biomarkers are still needed for an effective unified diagnostic strategy for AKI. Starting from previous and recent publications on the benefits and limitations of validated biomarkers responding to kidney injury, glomerular filtration and inflammation among others, this review unravels the role of new emerging biomarkers used alone or in combination, as reliable tools for early diagnosis and prognosis of CI-AKI, taking into account patients and procedures-risk factors towards a new clinical perspective.

Keywords: contrast-induced acute kidney injury; biomarkers; contrast media; nephrotoxicity

1. Introduction

Iodinated contrast drugs are widely used in diagnostics and surgical procedures. However, it is well established that contrast media (CM) exposure causes iatrogenic renal function impairment, which incidence is highly increasing, especially, in subjects with preexisting cardiovascular, diabetes or renal disease. Therefore, CM-associated kidney dysfunction variates from slight serum creatinine (SCr) increase to severe Acute Kidney Injury (AKI) [1–3]. AKI secondary to CM injection has historically been called contrast-induced nephropathy (CIN) or contrast-induced AKI (CI-AKI). Worryingly, the enormous burden of CM used in contemporary clinical practice explains why CI-AKI is one of the top leading forms of hospital-acquired renal disease, being in fact, the third most common cause of AKI [4]. To date, CI-AKI is defined as a rise in SCr of 0.5 mg/dL (or higher) or 25% (or higher) from baseline, occurring within the 2-3 days after the intravascular injection of iodinated

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radiographic CM, that cannot be attributed to other direct sources [1,2,5–10]. Additionally, AKIN (Acute Kidney Injury Network) and KDIGO (Kidney Disease Improving Global Outcomes) guidelines suggested a rise in SCr≥0.3 mg/dL with oliguria after hospitalization as a new standard to follow [6,11,12]. Since SCr is less accurate, it is better to define CI-AKI as a decrease in SCr clearance or estimated Glomerular Filtration Rate (eGFR) by 30-60 mL/min [1,7–9]. In some cases, CI-AKI may cause a more severe renal function impairment with progressive oliguria, requiring dialysis, which is associated with high mortality [1,7,10].

The overall incidence of CI-AKI is low, however, this rate increases critically in high-risk populations, where mortality is also higher [1–3,6–9,13]. Consequently, it is necessary to early identify those high-risk patients to avoid post-procedure renal function impairment, to guide precise therapeutic management, and hence, to improve patient outcomes. Besides, there is an extremely narrow window for intervention, increasing the risk of fatality.

For all these reasons, the identification and selection of specific urinary and/or serum biomarkers for early diagnosis of renal cell damage rather than functional impairment due to their high sensitivity and specificity, may overcome the limitations of SCr and urinary output (UO) as "*gold standard*" normalizing markers of CM-associated renal failure.

2. Pathophysiology of CI-AKI

Renal hemodynamic changes and nephrotoxic effects occur immediately after intravascular administration of iodinated contrast drugs and could last many hours to days. These unwanted side effects could be aggravated by intrinsic CM properties like osmolality and viscosity, but also due to concentration and volume administration. Generally, CM produces a rapid non-physiological vasodilatation followed by a long vasoconstriction, resulting in a prompt decrease in renal flow. This process results in a vicious cycle of medullary ischemia which causes, in turn, reactive oxygen species (ROS) generation and consequently, vascular endothelial and tubular injury [1,7]. Direct effects of kidney injury from exposure to CM are due to tubular epithelium toxicity substantiated by disruption of cell integrity, leading to loss of function, apoptosis, and eventually, necrosis. CM also increases blood viscosity, decreases microcirculation, and decreases urine flow rate, which increases the time that CM remains in the body and could produce microvascular thrombosis. All of this leads to an abrupt decrease in GFR, therefore, in kidney function [1,8,10] (Figure 1). Notwithstanding the above, the diagnosis of CI-AKI in clinical practice could be catastrophically delayed, as it is radically based on the identification of a late elevation of SCr and/or a decrease in eGFR. Consequently, this delay in diagnosis which places patients at high risk of progressive kidney damage, highlights the critical need to identify other blood and/or urine sensitive and specific biomarkers of incipient tubular injury, leading to rapid prognosis and diagnosis of CI-AKI development.

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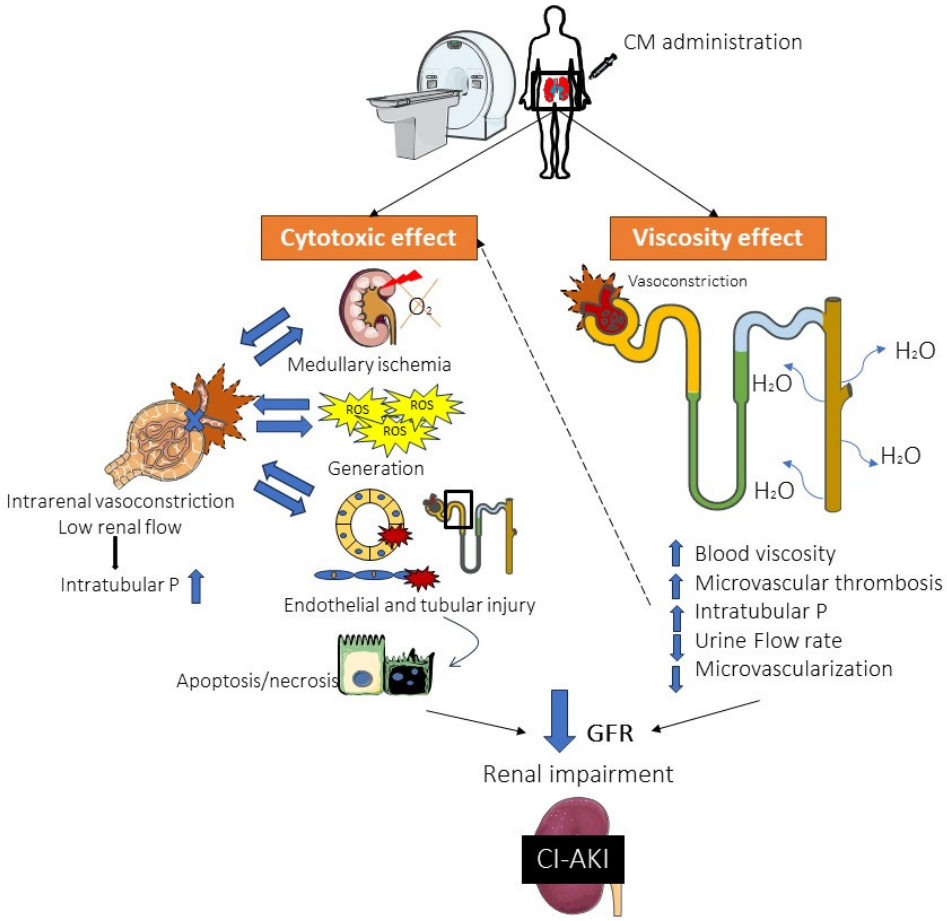

Figure 1. Contrast-induced acute kidney injury (CI-AKI) pathophysiology. Contrast media (CM) mediates on the other hand, direct renal tubular and endothelial cytotoxicity, leading to increased intrarenal pressure and consequent increase of intratubular pressure, resulting in a vicious cycle of medullary hypoxia, oxidative stress and increased loss of function, integrity and cell death. On the other hand, the viscous properties of CM trigger vasoconstriction, increases blood viscosity that reduces urinary flow rate, decreases microvascularization and increases the risk of microvascular thrombosis. All this leads to an abrupt loss of renal function resulting in CI-AKI. P, pressure; ROS, reactive oxygen species; GFR, glomerular filtration rate.

3. Traditional "*Gold Standard*" Markers

Traditionally, the RIFLE (Risk, Injury, Failure, Loss, End-Stage Kidney Disease), AKIN and KDIGO guidelines recommend the use of classic markers for AKI diagnosis and management. However, increased levels of these markers suggest functional changes, not kidney damage [14]. Despite this, the reliability of these markers is questioned and still controversial due to their lack of specificity and sensitivity, and high variability [15]. Worryingly, when these parameters are measurable in serum or urine, at least, 50% of the renal function may be lost [16]. Taken together, these reasons compel us to consider these obsolete markers as "data normalizers" for new accurate biomarkers of kidney injury.

3.1. Serum creatinine (SCr)

The diagnosis of CI-AKI is commonly based on an absolute (≥0.5 mg/dL) or relative (≥25%) increase in SCr within 48-72 hours after intravascular CM administration [5]. Consequently, changes in SCr are used to estimate acute changes in renal function and SCr monitoring, remains the

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cornerstone for CIN diagnosis. Unfortunately, this confirms that SCr is the most widely used and accepted biomarker by nephrologists and the scientific community. However, SCr is not an adequate marker of renal function, mainly because there is no correlation between SCr and actual kidney function under nonstationary conditions. Thus, SCr becomes a retrospective, late, insensitive and misleading measure of kidney damage [16].

3.2. Glomerular filtration rate (GFR)

Commonly, renal function is defined as the filtration capacity of the kidney, which could be expressed as GFR. However, GFR does not cover all kidney function which also involves glomerular permeability, tubular function, and several specific functions, such as vitamin D metabolism and erythropoietin production [17]. In addition, GFR could be estimated (eGFR) based on the empirical Cockcroft-Gault, MDRD (Modification of Diet of Renal Disease) or CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formulas [18,19], which involve SCr levels as a common variable. Currently, patients with CI-AKI are diagnosed with an eGFR of 30-60 mL/min [7]. However, the latter issue is of particular importance, as changes in SCr lag behind changes in GFR, leading to the possibility of progression of AKI stage despite actual improvement in renal function, a shortcoming that could be overcome with the availability of real-time assessment of GFR [20]. For this reason, the aforementioned concerns about SCr may also apply to the determination of GFR, as the interpretation of changes using one parameter alone is difficult. However, two recent clinical trials established the primary endpoint of drug efficacy by Iohexol plasma clearance-based GFR and by serum cystatin-based (eGFRecys), respectively [21,22].

3.3. Urinary Output (UO)

Nephrologists recognized UO as the most sensitive system for determining CI-AKI. Due to some limitations, it is not regularly used in the clinical setting, as it requires regular urine collection and catheterization of the patient. Surprisingly, in a retrospective study, UO captured >40% AKI results than SCr [23].

4. Novel Biomarkers: The necessity for a precise CI-AKI diagnosis

In recent decades, the identification of new biomarkers of AKI has been the subject of interest by scientists worldwide. However, the predictive, diagnostic and prognostic ability of biomarkers in the context of iodinated contrast administration, has been less studied. In recent years, many additional potential biomarkers have been newly described for the early detection of tubular dysfunction/lesion associated with CM administration, to reliably measure CI-AKI, and thus prevent patient outcomes. Some of them are well characterized and categorized and could be divided into different groups in response to different physiological conditions: some involved in glomerular filtration, others related to the inflammatory response and tubular cell injury or with a not well-defined relationship with the disease and new emergent biomarkers under study. Figure 2 schematically represents the traditional and novel biomarkers described for CI-AKI.

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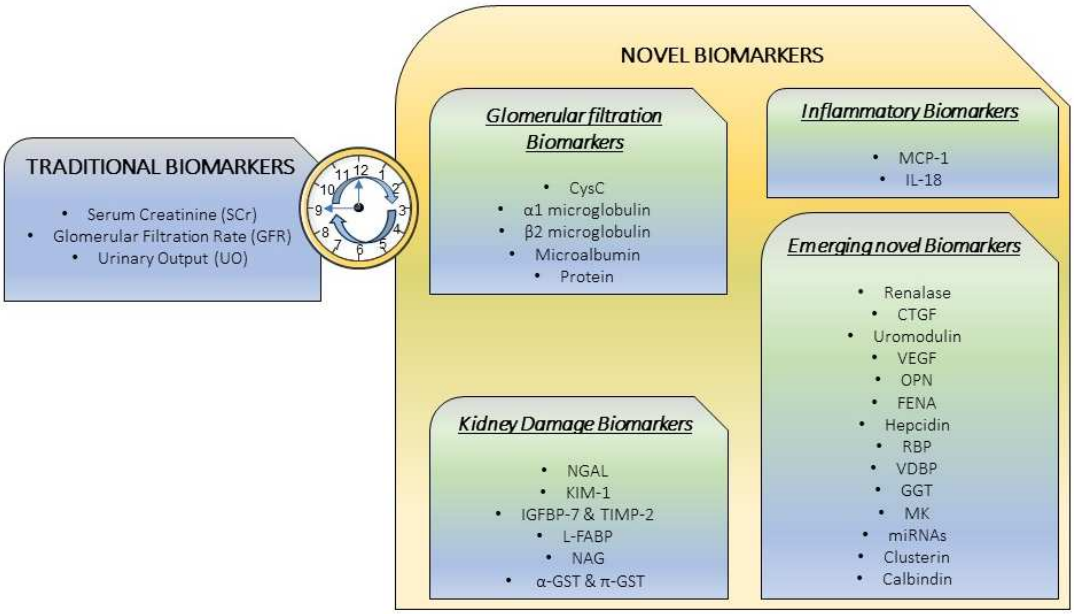

Figure 2. Traditional and novel biomarkers classification. *CysC*, Cystatin C; *NGAL*, Neutrophil Gelatinase-Associated Lipocalin; *KIM-1*, Kidney Injury Molecule-1; *IGFBP*, Insulin-like Growth Factor-Binding Protein; *TIMP*, Tissue Inhibitor of Metalloproteinase; *L-FABP*, Liver Fatty Acid-Binding Protein; *NAG*, N-Acetyl-β-D-Glucosaminidase; *GST*, α-Glutathione S-Transferase; *MCP-1*, Monocyte Chemoattractant Protein-1; *IL*, Interleukin; *CTGF*, Connective Tissue Growth Factor; *VEGF*, Vascular Endothelial Growth Factor; *OPN*, Osteopontin; *FENA*, Fractional Excretion of Sodium; *RBP*, Retinol Binding Protein; *VDBP*, Vitamin D Binding Protein; *GGT*, Gamma-glutamyltransferase activity; *MK*, Midkine; *miRNAs*, microRNA.

4.1. Glomerular filtration biomarkers

4.1.1. Cystatin C (CysC)

CysC is a small molecule freely filtered by the glomerulus, and subsequently reabsorbed and metabolized by the proximal tubule [24]. Compared with SCr, serum CysC concentration (sCysC) is less dependent on age, gender, muscle mass and nutrition and therefore, more reliably predicts deterioration of renal function, becoming a sensitive marker of kidney injury. An increase in sCysC levels reflects a decrease in GFR and therefore, there is an inherent delay between renal injury and a detectable increase in its levels [25]. Thus, sCysC increases more rapidly than SCr when GFR decreases [14,15]. CysC is usually undetectable in the urine of patients with normal renal function; however, tubular injury could result in measurable urinary levels, suggesting urinary CysC as a potential biomarker for AKI [25,26].

Regarding CI-AKI, the study of CKD patients undergoing coronary (CA) or peripheral angiography demonstrated that increased sCyC is a reliable marker to rule out CI-AKI and an independent predictor of death and dialysis [14,27,28]. Complementary studies in patients undergoing coronary angiography and/or therapeutic percutaneous coronary intervention (PCI) showed that sCysC is incremented 24 hours after CM application, and this correlated with CI-AKI and was associated with a higher incidence of adverse events at one year [8,29–33]. Finally, a recent publication stated that sCysC at 24 hours was the best biomarker for CIN diagnosis, while baseline levels of other common biomarkers were the best predictors of prognosis [34].

4.1.2. α1-Microglobulin (α1-m)

α1-m is a member of the lipocalin family of proteins that is synthesized in the liver, freely filtered by glomeruli and reabsorbed by the renal proximal tubular cells, where it is catabolized. The α1-m

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form is stable and, under normal conditions, appears very poorly filtered in the final excreted urine [35]. Therefore, urine levels above the reference values could indicate proximal tubular damage, resulting α1-m as a preferred biomarker. Terzi *et al.* showed that α1-m can early predict the development of sepsis-associated AKI (SA-AKI) in critically ill patients by ensuring proximal tubular dysfunction [35]. Furthermore, a recent study concluded that α1-m is a suitable biomarker for early-stage kidney injury detection after cardiac surgery [36].

4.1.3. β2-Microglobulin (β2-m)

β2-m is a little protein, expressed on the cell surface of every nucleated cell and which is filtrated by the glomerulus and almost all β2-m proteins have undergone reabsorption and catabolism by the proximal tubular cells [15]. Increased levels of β2-m excretion in urine have been described as an early sign of tubular dysfunction due to many causes, such as exposure to nephrotoxic substances, cardiac surgery and renal transplantation, preceding by 4-5 days the rise in serum creatinine levels. However, the disadvantage of β2-m as a biomarker is its instability in the urine and fast degradation in room temperature and urine with pH <6.0 [37]. Recent publications suggest that β2-m could be a suitable biomarker for predicting prognosis in CI-AKI [34,38].

4.1.4. Microalbuminuria

The term microalbuminuria indicates urinary albumin at a concentration that is below the threshold for albumin detection by conventional measurement protocols and its value ranges between 30-300 mg/L [15]. It is suggested to be an important marker of glomerular structure and function alterations and it was designated as a biomarker to investigate the attenuation of CI-AKI by N-acetylcysteine [39]. In addition, a recent clinical study shows that increased preprocedural urinary microalbumin is associated with a high risk of renal deterioration after CA [40].

4.1.5. Proteinuria

Increased urinary protein excretion (proteinuria) is the result of alterations in the glomerular filtration barrier, generally associated with specific podocyte damage. Therefore, total urinary protein has been highlighted as a diagnostic marker and as a predictive factor for progressive loss of renal function in clinical and non-clinical settings [41–43]. Specifically, in CI-AKI it has been demonstrated that protenuria is an important risk factor and an independent indicator of 1-year mortality in patients with cerebrovascular disease [44].

4.2. Inflammatory biomarkers

4.2.1. Monocyte Chemoattractant Protein 1 (MCP-1)

MCP-1 is a potent chemotactic factor for monocytes and macrophages involved in ischemic and toxic AKI. However, its potential use as a biomarker has been less well studied. Several studies have shown that urinary MCP-1 expression (uMCP-1) is increased in both murine models and in patients with kidney injury [45]. Additionally, recent studies have shown that uMCP-1 in combination with other markers (e.g., epidermal growth factor –EGF-, kidney injury molecule-1 -KIM-1-, neutrophil gelatinase-associated lipocalin –NGAL-) appears to represent a potent diagnostic and prognostic biomarker of tubulointerstitial injury and repair [16,45–47]. Therefore, MCP-1 alone or in combination with other molecules, could be considered a useful biomarker in AKI, which could also be extrapolated to CI-AKI.

4.2.2. Interleukin 18 (IL-18)

IL-18 is a pro-inflammatory cytokine released by proximal tubular epithelial cells in response to injury. After kidney injury, IL-18 is massively secreted into the urine and increases in the first 6 to 12 hours before a significant decline in renal function and remains elevated for up to 48 hours [25]. Human studies demonstrated that urinary IL-18 (uIL-18) levels were significantly higher in patients

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with AKI than in those without AKI at 24 and 48 hours before SCr increased [43,48,49]. Surprisingly, a similar study in elderly patients undergoing gadolinium-enhanced magnetic resonance imaging (MRI) displayed an increase in uIL-18 after CM administration for 24 hours, compared to a delayed increase in SCr levels [50]. However, several clinical performed to evaluate new diagnostic biomarkers of CI-AKI following CA or PCI, indicated that no statistically significant differences in uIL-18 were observed in patients with CI-AKI compared to patients without CI-AKI; neither were significant changes observed between uIL-18 before and after the intervention [51,52].

4.3. Kidney damage biomarkers

4.3.1. Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is a protein of the lipocalin family that covalently binds to neutrophil gelatinase and is dramatically upregulated in the kidneys after ischemic or toxic damage [53,54]. NGAL has been shown to decrease apoptosis and increase tubular cell proliferation, favoring renal tissue recovery after damage. This particular role may explain the sustained elevated urinary NGAL (uNGAL) levels observed during the days following renal injury [55]. Therefore, NGAL may also be detected in the proximal tubular epithelium due to the failure of reabsorption of filtered NGAL [56].

Surprisingly, NGAL increases rapidly in a dose-dependent manner and is detectable at early points (3 hours after kidney damage and peaks at 6-12 hours). Moreover, its elevation could persist markedly for up to 5 days if the initial injury is severe. For this reason, among all new biomarkers, NGAL is one of the most widely investigated.

One of the most ambitious studies based on large cohorts of patients, both children and adults, receiving contrast agents and undergoing cardiac catheterization, intra-arterial coronary angiography or computed tomography (CT), revealed a very good performance of plasma and uNGAL in the prediction of CI-AKI [57,58].

More recently, uNGAL monitoring studies revealed that NGAL also predicted the severity of CI-AKI into CKD and/or hemodialysis progression, demonstrating that NGAL is potentially superior compared to conventional markers of nephropathy after invasive coronary procedures with contrast agents [59–63]. However, ANTI-CI-AKI clinical trial study concluded that uNGAL was not able to predict CI-AKI and was an inadequate tool to guide an early intervention strategy to prevent CI-AKI outcomes [64] and further studies will be necessary.

4.3.2. Kidney Injury Molecule 1 (KIM-1)

KIM-1 is a type I transmembrane glycoprotein that is poorly expressed in the kidneys of healthy subjects. However, following ischemia/reperfusion injury (IRI) and nephrotoxic exposure, KIM-1 is dramatically overexpressed in the proximal tubular epithelium in both rodent models [65,66] and humans [67]. Following kidney injury, the extracellular domain of KIM-1 is released from the tubular epithelial cells in a metalloproteinase-dependent manner. This release, in combination with the persistent increase of renal KIM-1 synthesis, leads to a rapid increase in exclusively urinary KIM-1 after 48 hours [68].

Recent clinical studies have shown that urinary KIM-1 concentration (uKIM-1) is higher in patients with AKI due to ischemia and hypoperfusion, nephrotoxins, CIN nephropathy and cardiac surgery compared to controls, and also that it is a predictor of the risk of developing AKI [69–71]. Since KIM-1 is defined as an effective early biomarker in AKI, several rodent models showed that uKIM-1 concentration was elevated 12 hours following CM administration [72,73]. Furthermore, differences in uKIM-1 production were found in pre-existing kidney injury models of hypertension, diabetes and nephropathy subjected to CM administration [74]. Multiple human clinical studies confirm the potential use of uKIM-1 as an early valuable marker for CIN diagnosis. In a large study of more than 3000 patients undergoing CA, KIM-1 levels were found to be significantly increased in the urine of CIN patients at the sixth hour compared to baseline [75]. These results confirmed a previous study in which KIM-1 was measured 12 hours after cardiac catheterization in humans and exhibited a good predictive value for CI-AKI diagnosis with high sensitivity and specificity [76].

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4.3.3. Insulin-like Growth Factor-Binding Protein 7 (IGFBP-7) and Tissue Inhibitor of Metalloproteinases-2 (TIMP-2)

IGFBP-7 and TIMP-2 are master regulatory biomarkers of G1 cell cycle arrest, predominantly expressed in proximal and distal tubular cells in response to DNA damage. Unlike many previously studied biomarkers, both are markers of cellular stress in an early phase of tubular cell damage caused by a wide variety of triggers and could act as a protective mechanism for cell injury [77,78]. Remarkably, these two proteins are discussed in combination because some preclinical studies demonstrated their superiority when used together to predict advanced AKI stages compared to other biomarkers [79].

In 2014, the FDA approved the first point-of-care device (NephroCheck test) that allows the determination of both urinary IGFBP-7 and TIMP-2 in critically ill patients with an increased risk of developing moderate-to-severe AKI. The NephroCheck test anticipates the diagnosis of AKI, therefore reducing the social and health care costs associated with worsening disease in these patients [80,81]. Surprisingly, other clinical and observational studies reported that the combined IGFBP-7/TIMP-2 test was the strongest predictor of AKI and significantly improved the risk assessment after major surgery [81]. Despite this, the impact of CM on these biomarkers and the evaluation of the potential development of CI-AKI have not yet been addressed.

4.3.4. Liver Fatty Acid-Binding Protein (L-FABP)

L-FABP is a protein that is expressed in several tissues, but predominantly localizes to the renal proximal tubule epithelium and is excreted into the tubular lumen before binding to peroxisomal toxic products [82–84]. Urinary L-FABP (uL-FABP) has been extensively studied in preclinical and clinical models and has been suggested as a potential biomarker in a variety of pathological conditions, such as AKI, CKD, diabetic nephropathy, IgA nephropathy and CI-AKI [85,86].

Nakamura et al. demonstrated that uL-FABP increase was associated with CIN. Remarkably, before angiography, uL-FABP concentration was significantly higher in 13 of 66 patients suffering from CIN compared to the non-CIN group or healthy volunteers [87], suggesting that uL-FABP levels could clinically serve as a useful predictive biomarker to detect CI-AKI onset before CM exposure.

4.3.5. N-acetyl-β-d-glucosaminidase (NAG)

NAG is a lysosomal enzyme that is expressed mainly in the brush border of proximal renal tubular cells but also is localized in the liver, brain and spleen [88]. Due to its nature, NAG does not cross the glomerular barrier and therefore, urinary NAG release reflects tubular impairment.

Increased NAG levels have been described in multiple AKI onsets showing, in all cases a high sensitivity for detecting AKI [88–91]. However, increased NAG levels have been reported in a variety of non-clinical AKI conditions, limiting the use of NAG as a marker of AKI in some settings [92].

Comparative investigations suggested that NAG is also a valuable biomarker in CI-AKI, exclusively in patients undergoing CA and/or therapeutic PCI. A robust study showed that urinary NAG (uNAG) and sCr were significantly increased on days 1 and 2 after radiocontrast injection, compared to patients without CI-AKI. Moreover, uNAG levels peaked earlier and increased more than sCr levels [93]. Clinical studies in children corroborated that uNAG detection may contribute to a more accurate diagnosis of CI-AKI by indicating increased stress on the kidneys after CA [94,95].

4.3.6. α, π glutathione S-transferase (α-GST, π-GST)

α-GST and π-GST are promising proximal and distal tubular cytosolic enzymes respectively, that are considered promising biomarkers for early detection of AKI. In AKI, a single urinary π-GST measurement performed better than α-GST at predicting dialysis requirement or death, whereas α-GST performed better in patients with AKI in stage 1 or 2. However, neither marker had good prognostic discrimination [96]. Finally, further other investigations showed that urinary GSTs predicted AKI progression or hospital mortality after cardiovascular surgery, where CM

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administration is correlated with kidney damage following an increase in urinary biomarkers [97–99].

4.4. Emerging novel biomarkers

Among the classical CI-AKI biomarkers, a large number of promising molecules have been constantly investigated to assess their predictive and intrinsic diagnostic value in a wide spectrum of renal disorders, including CI-AKI, to improve patient outcome. However, some of them are exclusively studied in animal models although some are not yet in CI-AKI models. Hence, there is an open need to discover, evaluate and validate the best-performing biomarkers in clinical trials, and, consequently, to extrapolate them to clinical practice. These include:

4.4.1. Renalase

Renalase is a novel catecholamine-metabolizing amine oxidase synthesized mainly by proximal tubular cells and secreted into the urine and bloodstream, which plays a key role in blood pressure regulation [100]. In animal models, renalase-deficient mice displayed a severe IRI reflected by higher SCr and a significant increase in tubular inflammation, apoptosis and necrosis, which was partially alleviated by renalase pretreatment [101]. Renalase was also documented to ameliorate cisplatin-induced AKI [102].

Singularly, a recent study of ioversol-induced CI-AKI showed an exceptional protective effect of renalase pretreatment on renal function and kidney morphology in rats [103]. To date, only one clinical study is available to evaluate the urinary renalase concentration in patients with preserved renal function undergoing CA/PCI interventions, in which it was observed that their urinary levels were reduced after these interventions [103]. However, further studies will be required to validate renalase as a diagnostic marker of CI-AKI, and also to assess that the exogenous recombinant renalase administration could serve as a preventive therapeutic agent [104,105].

4.4.2. Connective Tissue Growth Factor (CTGF)

CTGF is an important profibrotic factor that is upregulated in kidney diseases. When endogenous CTGF is artificially suppressed in experimental models of kidney injury, renal function is restored [106]. In a murine model of CI-AKI, CTGF gene expression levels increased 2 days after CM administration in nephrectomized mice compared to the non-CM infusion group [107]. Despite this, clinical correlations have not yet been addressed and further studies will be necessary to evaluate CTGF protein as a kidney injury biomarker in humans.

4.4.3. Uromodulin

Uromodulin, also known as Tamm-Horsfall protein, is a glycoprotein localized mainly in renal tubular cells lining the thick ascending limb of the loop of Henle. In the last decade, uromodulin has been implicated in the pathophysiology of several diseases, including AKI and CKD, showing a protective role through downregulation of interstitial inflammation [108]. Surprisingly, several publications expressed an exponential interest in the role of uromodulin in CM nephrotoxicity, showing a huge urinary decrease after CM administration in patients, but also in canine experimental models [109–111]. Recent publications have demonstrated that a lower uromodulin-to-creatinine ratio is associated with AKI after cardiac surgery. Overall, the consideration of uromodulin as a biomarker in clinical measures could be considered to minimize the risk of developing AKI/CI-AKI [112,113].

4.4.4. Vascular Endothelial Growth Factor (VEGF)

VEGF is an endothelial-specific growth factor that promotes endothelium proliferation, differentiation, survival and mediates vasodilatation, microvascular permeability and matrix remodeling. In the kidney, it is prominently expressed in tubular epithelial cells and glomerular

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podocytes and is associated with the pathophysiology of diabetic nephropathy, glomerulosclerosis and tubule-interstitial fibrosis [114].

Despite the lack of updated clinical results regarding CI-AKI, a single study of CM administration in rats suggested that VEGF protein levels in kidney tissue were significantly higher compared to controls and consequently, it was correlated with advanced kidney damage. Interestingly, paricalcitol pretreatment ameliorated kidney injury markers, including VEGF levels, thus offering the opportunity to prevent CI-AKI [115].

4.4.5. Osteopontin (OPN)

OPN is a glycoprotein expressed in bone, immune, smooth muscle, epithelial and endothelial cells and plays an important role in bone mineralization and resorption. In addition, OPN is found in the kidneys and urine and its expression results elevated in several renal pathologies [116], suggesting its potential role as a novel biomarker. Besides this, clinical trials and observational studies demonstrated that OPN had a positive association with the risk of AKI in patients undergoing CA [117] and could predict the patient outcome after cardiac arrest [118].

4.4.6. Fractional Excretion of Sodium (FENa)

FENa is the percentage of the sodium filtered by the kidney that is excreted in the urine. Principally, under normal conditions, most of the sodium is reabsorbed by intact tubular cells, but another small part is excreted in the urine. Therefore, FENa could be calculated to assess changes in renal blood flow and kidney tubular damage under pathological conditions [119].

In a clinical study, it was observed that patients with oliguric AKI presented <1% FENa in pre-renal AKI and >3% in acute tubular necrosis (ATN), demonstrating the applicability of FENa as a prognostic marker [119]. Subsequently, different studies were conducted to evaluate the effects of CM exposure in human kidneys, indicating that CM administration is associated with increased urinary FENa [120,121]. These findings were also corroborated in animal models [122,123].

4.4.7. Hepcidin

Hepcidin is a small peptide hormone principally produced in hepatocytes, but also in other tissues such as the kidney or brain. In the kidney, hepcidin is freely filtered by the glomeruli with significant tubular uptake and catabolism, which could be excreted in the urine and also found in plasma [124]. Surprisingly, clinical researchers determined that lower levels of hepcidin could predict the risk for AKI development [125–127]. However, in patients undergoing PCI, serum hepcidin concentration increased at 4 and 8 hours after CM administration, while urine hepcidin was significantly lower in PCI patients with CI-AKI compared with baseline [128]. Consequently, early changes in hepcidin could predict a later CI-AKI onset.

4.4.8. Retinal Binding Protein (RBP)

RBP is a carrier protein filtered mainly by the glomeruli and reabsorbed by the proximal tubules of the kidney. The relation of variation in serum RBP levels was initially studied in a small cohort of patients with kidney disease and healthy volunteers, in whom the urinary concentration of RBP was differentially excreted, leading to the conclusion that RBP could be useful for the diagnosis and monitoring of kidney disease progression [129]. Accordingly, in a randomized controlled study, urinary RBP concentration was rapidly elevated in patients undergoing peripheral arterial angiography [130].

4.4.9. Vitamin D Binding Protein (VDBP)

VDBP is filtered in the glomerulus, reabsorbed by proximal tubule epithelial cells and subsequently catabolized, thus reducing urinary excretion. After tubular injury, increased urinary VDBP (uVDBP) levels are expected to be found, reflecting renal damage. Chaykovska *et al.* demonstrated that uVDBP is a potent biomarker of major renal adverse effects after CA intervention,

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concluding that uVDBP concentration 24 hours after CM administration was predictive for dialysis and death [131].

4.4.10. Gamma Glutamyl Transferase (GGT)

GGT is an enzyme localized in the brush border of the renal proximal tubules that appears in the urine (uGGT) when damage occurs. Early clinical studies focused on tubular toxicity due to CM exposure showed a relevant early increase in uGGT enzyme activity in patients undergoing radiological examination with intravascular injection of CM [132]. Recently, the same results were obtained in patients undergoing PCI, where urinary GGT showed a predictive value for CI-AKI progression [133].

4.4.11. Midkine (MK)

MK is a heparin-binding growth factor that regulates inflammation, cell growth, survival and migration. In the kidney, MK is expressed in both proximal and distal tubular epithelial cells. Strikingly, MK was found to be significantly elevated 2, 4, and 8 hours after CM exposure, exclusively in patients undergoing PCI, and then, returned to baseline after 24 hours and started to decrease after 2 days [134], suggesting MK determination as a great opportunity for CI-AKI treatment.

4.4.12. MicroRNAs (miRNAs)

miRNAs are short, non-protein-coding RNA molecules that regulate gene expression at the post-transcriptional level by mRNA repression and are involved in multiple cell mechanisms, such as proliferation, differentiation, death or inflammation. For this reason, miRNAs differential expression is principally related to pathophysiological conditions, including kidney injury [15,135]. Among others, miR-21 has been extensively studied in the kidney, where it plays a crucial role in cell proliferation and downregulation of apoptosis after renal IRI [136], while serum and urine levels of miR-21 also predict AKI in cardiac surgery patients [137]. In particular, different preclinical studies that were validated in humans revealed that circulating levels of miR-188, miR-30a, miR-30c and miR-30e should be considered as early biomarkers in CI-AKI [138].

4.4.13. Clusterin

Clusterin is a sulfated glycoprotein mainly present in the cytoplasm of proximal and distal convoluted tubules [139]. In the context of kidney injury (nephrotoxicity, ischemia, surgery) in experimental models, it has been suggested that clusterin could play an anti-apoptotic role in favoring cell protection and regeneration [140].

In a variety of nephrotoxic models including cisplatin, higher urinary levels of clusterin outperformed BUN and SCr for detecting proximal tubular injury even in the absence of functional effects and was correlated with positive clusterin kidney immunostaining [140,141]. Interestingly, in ischemia-reperfusion models, clusterin deficiency worsens renal inflammation and kidney fibrosis after IRI, suggesting a crucial role in kidney cell repair and proliferation [142,143]. Despite the lack of studies indicating the predictive potential value of clusterin in CI-AKI, a controlled clinical trial performed by Da *et al.* has been recently published, suggesting for the first time that clusterin could detect early nephrotoxicity and predict AKI when compared AKI cases with non-AKI controls [144]. This study opens the possibility of using clusterin as a future biomarker in CI-AKI.

4.4.14. Calbindin

Calbindin is an intracellular protein involved in the regulation of calcium reabsorption that is commonly expressed and localized in the distal tubule and the proximal part of the collecting ducts. As a kidney injury marker, calbindin has been studied in rat and sheep nephrotoxic models, thus reflecting changes in urinary excretion without histological alterations [145,146]. In humans, calbindin concentration was significantly higher in urine from patients receiving cisplatin chemotherapy while SCr levels remained unchanged [147,148]. In correlation, calbindin was the most

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consistently and significantly altered urinary marker in patients following partial nephrectomy, suggesting its potential role as an early predictor of AKI and CI-AKI [149], although future studies will have to be developed to demonstrate its effectiveness.

5. Combination of Biomarkers: a Future Approach

To date, most preclinical and clinical studies on kidney diseases only validate one biomarker rather than a combination of several, limiting the ability to determine whether several specific panels of biomarkers are more specific and predictive than one biomarker alone. Biomarker combinations could be integrated into clinical practice using viable high-throughput technology to increase the ability to detect and diagnose multiple renal disorders early, unravel new pathophysiological mechanisms and consequently, prevent undesirable long-term patient outcomes.

Vaidya et al. suggested that comparative values of multiple urinary biomarkers detection (NGAL, Hepatocyte Growth Factor (HGF), VEGF, Protein and KIM-1) were associated with sensitive and specific prognosis and diagnosis of AKI in humans [92]. Furthermore, in a cross-sectional study, the combination of urinary Matrix Metalloproteinase 9 (MMP-9), KIM-1 and NAG markers allowed AKI diagnosis earlier than an increase in SCr [69]. However, the results of the SAPHIRE study demonstrated that performing exclusively urinary TIMP-2/IGFBP7 significantly improved AKI risk stratification, thus providing additional information on clinical variables [79]. In a cohort study based on major surgeries, it was proposed that urinary NGAL and L-FABP determination may improve the diagnostic yield of AKI [150]. In addition, the combination of urinary IL-18 and KIM-1 concentrations had a very good predictive value for predicting AKI stage 3 or death, thus identifying high-risk patients after cardiac surgery [151]. Moreover, in studies on obstructive nephropathy and cisplatin-induced nephrotoxicity, the combined detection of the EGF/MCP-1 ratio, urinary NGAL and urinary KIM-1 outperformed that of any of the biomarkers alone in predicting progressive renal damage, thus, avoiding undesirable long-term outcomes [46,47]. Finally, several recent investigations focusing on contrast-induced nephrotoxicity deciphered multiple biomarker combinations that successfully predicted early CI-AKI, predominantly in patients undergoing CA. While Wybraniez *et al.* proposed that post-procedural determination of urinary KIM-1 and IL-18 predicted CI-AKI; Connolly *et al.* suggested that serum L-FABP and plasma NGAL were the best combination to predict early CI-AKI [52,152]. Finally, Banda *et al.* stated that serum CysC at 24 hours was the best biomarker for CIN diagnosis, while baseline levels of serum IL-18, β-2M and TNFα were the best for predicting prognosis [34].

6. Conclusions

Iodinated contrast drugs are widely used in various clinical procedures, increasing the patient's risk of mild to severe kidney alterations and the development of CI-AKI. The absence of current pharmacological treatments for AKI makes intensive care the only possible supportive tool and, therefore, new emerging therapeutic approaches are greatly needed.

However, so far there is no consensus among experts on which biomarker panel neither for AKI nor for CI-AKI diagnosis and prognosis. This is of great concern because the lack of well-established worldwide clinical guidelines for CI-AKI prevention and management, could be detrimental to patient recovery and survival. Therefore, we envision a clinical setting in which a single urine/plasma preparation will be rapidly analyzed for simultaneous measurement of a stringent panel of desired biomarkers for kidney disease, using a validated and cost-effective high-throughput assay that allows for rapid in-hospital patient monitoring, thus preventing patients from suffering poor outcomes and improving renal therapies.

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Data Availability Statement: No new data have been created in this review article, only a review of the state of the art of biomarkers in acute renal failure-induced by iodinated contrast agents, and all the data noted have been extracted from the relevant literature in the article.

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