Review

Renalase and Biomarkers of Contrast-Induced Acute Kidney Injury

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Key Words

Renalase · Contrast-induced acute kidney injury · Biomarkers

Abstract

Background: Contrast-induced acute kidney injury (CI-AKI) remains one of the crucial issues related to the development of invasive cardiology. The massive use of contrast media exposes patients to a great risk of contrast-induced nephropathy and chronic kidney disease development, and increases morbidity and mortality rates. The serum creatinine concentration does not allow for a timely and accurate CI-AKI diagnosis; hence numerous other biomarkers of renal injury have been proposed. Renalase, a novel catecholamine-metabolizing amine oxidase, is synthesized mainly in proximal tubular cells and secreted into urine and blood. It is primarily engaged in the degradation of circulating catecholamines. Notwithstanding its key role in blood pressure regulation, renalase remains a potential CI-AKI biomarker, which was shown to be markedly downregulated in the aftermath of renal injury. In this sense, renalase appears to be the first CI-AKI marker revealing an actual loss of renal function and indicating disease severity. **Summary:** The purpose of this review is to summarize the contemporary knowledge about the application of novel biomarkers of CI-AKI and to highlight the potential role of renalase as a functional marker of contrast-induced renal injury. **Key Messages:** Renalase may constitute a missing biochemical link in the mutual interplay between kidney and cardiac pathology known as the cardiorenal syndrome.

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Introduction

Up to the present time, no acute kidney injury (AKI) marker has been able to identify patients with contrast-induced AKI (CI-AKI) at an early stage. This complex form of cardiorenal syndrome type 1 combines the nephrotoxic impact of contrast media (CM) on renal tubules with the deleterious effect of hemodynamic instability [1, 2]. The enormous burden

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of CM used in contemporary cardiology practice explains why CI-AKI became the third leading form of hospital-acquired renal failure [2]. Despite its benign clinical manifestation, preserved urine output and transient course, CI-AKI translates into extended hospitalization time, greater costs of health care services [3] and, most importantly, increased in-hospital morbidity, the risk of a consolidation of the kidney injury as chronic kidney disease (CKD), the need for chronic renal replacement therapy and increased short- and long-term mortality rates [4]. Only just recently has the HORIZONS-AMI substudy revealed a devastating impact of CI-AKI on the composite endpoint of bleeding and adverse cardiovascular events, as well as on the 30-day (8.0 vs. 0.9%; $p < 0.0001$) and the 3-year mortality rate (16.2 vs. 4.5%; $p < 0.0001$), in the narrow setting of ST-segment elevation myocardial infarction [5]. The financial aspect of the problem is best reflected in the estimated cost of treatment of 1 patient with contrast-induced nephropathy amounting to nearly USD 11,812 [3]. Still, the majority of CI-AKI incidents remain undiagnosed, since the routinely used serum creatinine concentration (SCr) is not elevated until 2–5 days following intervention. In the era of radial approach preference, the majority of patients are discharged prior to the creatinine diagnostic window, which precludes any accurate cardiovascular risk estimation related to CI-AKI incidents. To date, numerous biomarkers have been proposed; however, none of them entered daily clinical practice.

Renalase is a protein produced and secreted by proximal tubular cells which catabolizes catecholamines in the bloodstream, thereby lowering blood pressure [6]. The suppression of renalase synthesis and the resultant plasma renalase reduction in the acute phase of CI-AKI could serve as a loss-of-function marker and account for the deleterious long-term effects of acute renal compromise on the cardiovascular system underlying the cardiorenal syndrome. Moreover, polymorphisms of the renalase gene were essentially linked to cardiac hypertrophy, reduced left ventricular ejection fraction, impaired exercise tolerance and inducible myocardial ischemia in subjects diagnosed with stable coronary artery disease [7].

The purpose of this review article is to investigate into the different biomarkers of CI-AKI with a special focus on the possible role of plasma and urinary renalase as a marker and risk stratification tool of CI-AKI. Accordingly, the Medline and Embase databases were queried to obtain original research articles and review papers using the following key words: renalase, NGAL, cystatin C, L-FABP, IL-18, KIM-1, markers, contrast-induced acute kidney injury, CI-AKI, contrast-induced nephropathy and CIN.

Ideal Marker

The idea of the so-called renal troponin has driven the search for an ideal biomarker which could facilitate the early initiation of treatment such as intravenous hydration or renal replacement therapy. Markers of renal injury can be tested either in blood or in urine and potentially comprise substances which are (a) accumulated in blood secondary to reduced glomerular filtration and/or tubular secretion, (b) present in urine due to abnormal reabsorption by injured proximal tubular cells, (c) released from injured tubular cells into urine and/or blood or (d) upregulated in response to injury and secreted into urine and/or blood. Moreover, the ideal biomarker should allow for a differentiation between prerenal and intrinsically renal kidney injury, since contrast agents inflict damage mainly on tubular cells with a secondary reduction in glomerular filtration rate. In daily clinical practice, the etiology of kidney functional worsening in patients with acute coronary syndrome is frequently unknown and may be associated with both hemodynamic instability and CM use.

SCr is far from ideal for the diagnosis of CI-AKI, on account of the exponential relationship between glomerular filtration rate and SCr; it gradually accumulates in the bloodstream and

even requires up to 5 days to exceed the threshold of CI-AKI diagnostic criteria [8]. Of note, SCr exhibits significant day-to-day variability irrespective of the actual pathological stimulus [9]. It is also dependent upon numerous physiological variables such as body weight, age, gender or hydration status. Therefore, numerous novel AKI markers have been proposed with the intention to overcome these limitations. Crucial scientific evidence regarding novel biomarkers of CI-AKI is highlighted in table 1.

Cystatin C

As it is produced in all nucleated cells, cystatin C belongs to the subgroup of cysteine proteases. Its concentration in blood remains a more sensitive biomarker of AKI than SCr [10], particularly in the case of pediatric, senile and emaciated patients [11]. Cystatin C levels are relatively stable and remain so irrespective of covariates such as age, gender, body weight or nutritional status; however, they can be substantially altered in the event of thyroid disease, glucocorticoid use, active neoplastic disease and systemic inflammatory response. Due to its relatively small size of 120 amino acids, cystatin C is filtrated entirely through glomeruli and subsequently undergoes a complete reabsorption and degradation in proximal tubular cells [12]. A recent meta-analysis delivered evidence for the high predictive power of serum cystatin C assessed within 24 h after renal injury for all-cause AKI [13]. These data were corroborated for the contrast-induced nephropathy scenario in the largest study so far by Briguori et al. [14]. This report covered 410 consecutive patients with CKD undergoing coronary or peripheral angiography. A relative increase in serum cystatin C by >10% at 24 h had 100% sensitivity and 85.9% specificity for the prediction of CI-AKI (defined as an increase in SCr of >0.3 mg/dl at 48 h), simultaneously being a predictor of impaired long-term major adverse cardiac events during 1 year of observation (OR = 2.52; 95% CI: 1.17–5.41; $p = 0.02$) [14]. Yet, cystatin C performs well as a biomarker 24 h after renal injury, which clinically represents a major delay postponing adequate management. In light of the above-stated limitations of creatinine and cystatin C, the current investigation is mainly focused on structural markers that are directly released or secreted by renal tubular cells, which could resemble the clinical meaning of troponin in myocardial injury.

Neutrophil Gelatinase-Associated Lipocalin

The most broadly recognized representative of this subset of biomarkers is neutrophil gelatinase-associated lipocalin (NGAL, or lipocalin 2). Stored in nonspecific neutrophil granules, NGAL is a 21-kDa, calyx-shaped protein engaged in innate nonspecific immunity mechanisms against bacterial infections and secreted in response to toll-like receptor activation [15, 16]. Its bacteriostatic activity is based on its affinity towards bacterial iron-binding siderophores [17]. NGAL also acts as a growth and differentiation factor in the organogenesis of kidneys, exerting its impact on epithelial cells via activation of the E-cadherin gene [17]. Most importantly, both urinary and serum NGAL concentrations serve as real-time indicators of renal tubular inflammation [18]. In line with the ‘forest fire’ theory proposed by Mori and Nakao [18], the NGAL level does not correspond with the residual amount of functional nephrons but with the extent of inflamed renal tissue. Following cardiac catheterization with radiocontrast use, the NGAL concentration is significantly elevated after 2 h in blood and after 4 h in urine [19]. Extensive scientific data support the notion that urinary NGAL is a powerful diagnostic tool for CI-AKI. In a study based on 130 patients with estimated glomerular

Table 1. Main evidence concerning novel biomarkers of CI-AKI

Marker	First author [Ref.], year	S/U	Time point	CI-AKI definition	Patients, n	Cut-off	CI-AKI prediction	AUC
CysC	Briguori [14], 2010	S	24 h	≥0.3 mg/dl within 48 h or RRT	410	>10% ↑ from baseline	PPV 39% NPV 100%	0.92
NGAL	Bachorzewska-Gajewska [19], 2007	S	2 h	≥25% relative ↑ within 48 h	100	n/a	NGAL significantly higher in CI-AKI than in non-CI-AKI	n/a
		U	4 h			n/a		
	Tasanarong [20], 2013	U	6 h	≥0.3 mg/dl or ≥50% relative ↑ within 48 h	130	>117 ng/ml	Sensitivity 94% Specificity 78%	0.84
	Torregrosa [28], 2014	U	12 h	≥50% relative ↑ within 6 days	193	n/a	CI-AKI vs. non-CI-AKI: 105 vs. 19 ng/mg Cr; p < 0.001	0.96
L-FABP	Nozue [27], 2010	U	24 h	≥0.5 mg/dl or ≥25% relative ↑ within 72 h	96	n/a	CI-AKI vs. non-CI-AKI: 25.2 vs. 8.9 ng/ml; p = 0.04	n/a
	Torregrosa [28], 2014	U	12 h	≥50% relative ↑ within 6 days	193	n/a	CI-AKI vs. non-CI-AKI: 33.9 vs. 33.7 ng/mg Cr; p > 0.05	0.64
KIM-1	Torregrosa [28], 2014	U	12 h	≥50% relative ↑ within 6 days	193	n/a	CI-AKI vs. non-CI-AKI: 4.7 vs. 1.5 ng/mg Cr; p < 0.001	0.71
IL-18	He [31], 2014	U	6–48 h	≥0.5 mg/dl or ≥25% relative ↑ within 48 h	180	815.61 pg/ml at 12 h	Sensitivity 87.5% Specificity 62.2%	0.81

AUC = Area under the receiver operator characteristic curve for CI-AKI prediction; CysC = cystatin C; n/a = not assessed; NPV = negative predictive value; PPV = positive predictive value; RRT = renal replacement therapy; S/U = serum or urine; ↑ = increase.

filtration rates <60 ml/min referred for elective cardiac catheterization, Tasanarong et al. [20] reported that urinary NGAL above the threshold of 117 ng/ml as measured after 6 h had a sensitivity of 94%, a specificity of 78% and an area under the curve of 0.84 for predicting CI-AKI as well as its severity. A joint analysis of both urinary and serum NGAL concentrations 2 and 4 h following percutaneous coronary intervention, respectively, revealed that both modalities successfully detected CI-AKI development [19]. Liebetrau et al. [21] achieved comparable results; however, urinary NGAL elevation became statistically significant in CI-AKI patients only 24 h, but not 4 h, following CM administration. The NGAL assay still needs to be validated in high-volume studies concerning patients undergoing coronary interventions, since its cost is 5-fold higher than that of SCr measurement [22]. The ANTI-CIN study was designed to investigate the effectiveness of an intravenous hydration protocol in patients with elevated NGAL directly after coronary angiography with the intention of avoiding CI-AKI incidents [23].

Liver Fatty Acid-Binding Protein

Liver fatty acid-binding protein (L-FABP) is a small cytoplasmic protein expressed in liver and proximal tubular cells. Not only is it involved in the transport and metabolism of long-chain fatty acids [24], but it is also upregulated in response to renal injury and released into urine. Two separate reports provided convincing data that even a baseline elevation of urinary L-FABP prior to CM administration identifies patients in great danger of CI-AKI development [25, 26]. According to a plausible study by Manabe et al. [25] comprising 200 patients, urinary L-FABP ≥ 24.5 $\mu\text{g/g}$ creatinine was an independent predictor of CI-AKI development (OR = 9.1; 95% CI: 3.2–28.9). Also, the postprocedural rise in urinary L-FABP 24 h after CM exposure was considerably more profound in the CI-AKI group than in patients without renal functional worsening (25.2 ± 31.5 vs. 8.9 ± 16.3 ng/ml; $p = 0.04$), as stated by Nozue et al. [27]. Furthermore, in a recent study by Torregrosa et al. [28], urinary L-FABP concentration at 12 h was predictive of CI-AKI development; still, it was inferior to the urinary NGAL assay at this specific time point following contrast agent use. Unexpectedly, urinary L-FABP tends to remain elevated as long as 14 days after the contrast-related renal insult [29].

Interleukin 18

The injury inflicted on tubular cells by contrast agents through various mechanisms initiates a local inflammatory response. One of the crucial cytokines modulating the process of intrarenal inflammation is interleukin 18 (IL-18), which is secreted by injured tubular cells. IL-18 stimulates the infiltration and activation of both T and NK lymphocytes and the subsequent production of interferon- γ . IL-18 is released into urine as early as 6 h after the beginning of renal injury [15]. In this sense, CI-AKI simultaneously is a marker and a mediator of acute renal injury. This also extends to contrast-mediated renal compromise, since Ling et al. [30] showed that urinary IL-18 was significantly increased at 24 h in their CI-AKI group in comparison with patients without this complication. In a different cohort of 180 patients submitted to percutaneous coronary intervention [31], urinary IL-18 was insignificantly elevated at 2 h, but significantly increased 6 h following the procedure, in contrast to controls (mean concentration: 782.9 vs. 998.5 pg/ml; $p < 0.01$) [31]; this implies a more rapid surge of urinary IL-18 levels than previously thought [30, 31].

Kidney Injury Molecule 1

Kidney injury molecule 1 (KIM-1) represents a transmembrane glycoprotein located in proximal convoluted tubules [15]. This molecule is excessively expressed in proximal tubules in response to cellular injury and is endowed with phagocytic properties [32]. It should be noted that KIM-1 is measurable only in urine. In the animal-based model of contrast-induced nephropathy, urinary KIM-1 concentration was elevated 12 h following CM administration [32]. In the previously mentioned study by Torregrosa et al. [28], KIM-1 evaluated 12 h after cardiac catheterization in humans exhibited a good predictive value for CI-AKI diagnosis (area under the receiver operating characteristic curve 0.71) and even showed superiority to L-FABP.

Limitations of Novel Biomarkers

Despite numerous favorable reports, studies on biomarkers were usually low volume and nonrandomized, which precludes extensive application of their results. Not all reports confirmed their clinical utility, which is potentially related to the diversity of the CI-AKI diagnostic criteria applied as well as to the different time points of biomarker measurement. Presumably, a set of sequential biomarkers (biomarker panel) would allow for a precise early diagnosis of AKI [33]; however, to date this has remained a vague concept with no supporting clinical data. The intriguing question arises whether these biomarkers solve the issue of compromised outcomes of patients with CI-AKI following elective or emergent coronary angiographies. In the event of an early diagnosis, clinicians still do not have an efficient armamentarium against CI-AKI, barring intravenous hydration and renal replacement therapy techniques. All the molecules considered were shown not to have any hemodynamic effect except for an improved diagnostic power in CI-AKI prediction, which, however, still awaits validation in high-volume cohorts. Undoubtedly, the clinical scenario of CI-AKI represents a specific variant of the cardiorenal syndrome, a phenomenon of simultaneous cardiac and kidney pathology, which could not be simply explained by a pure hemodynamic relation. Inspired by this observation, the group directed by Desir [6] from the Yale School of Medicine conducted a fundamental investigation into a molecule concurrently expressed in the kidneys and myocardium, which led to discovery of renalase, a novel protein engaged in catecholamine turnover.

Renalase

Since its description in 2005, a lot of scientific data were gathered concerning the structure and function of renalase [6]. Renalase constitutes a flavoprotein (342 amino acids; molecular mass: 38 kDa) encoded by the RNLS gene located on chromosome 10q23, expressed mainly in the proximal tubules, myocardium, skeletal muscles, brain and small intestine [6, 34]. Out of 4 splice variants, only the human renalase 1 isoform is detectable in human blood [35].

The pivotal role of renalase consists in blood pressure control by means of the degradation of circulating catecholamines to aminochromes, both in blood and urine [36] (fig. 1). Its property of amine oxidase relies on flavin adenine dinucleotide and nicotine adenine dinucleotide and is related to the N-terminal amine oxidase domain (75–335 amino acids). It exhibits a higher affinity towards epinephrine than dopamine and norepinephrine (epinephrine >> L-DOPA > norepinephrine = dopamine). Unlike monoamine oxidases and catechol-ortho-methyltransferase, renalase is released into the bloodstream, and its catalytic reaction does not lead to urinary excretion of deaminated and/or methylated metabolites of

Fig. 1. Renal and plasma renin systems and their role in blood pressure regulation, sodium and phosphate excretion and tubular cell survival [6, 34, 35, 38–43, 56–60]. I. Renalase is chiefly produced by proximal tubular cells, supposedly in response to D_5R stimulation by circulating dopamine. A plasma excess of catecholamines inactivates reninase inhibitor and leads to a significant increase in plasma reninase activity, which, in turn, triggers catecholamine degradation into aminochromes. Renalase mediates cardiomyocyte survival and protects against ischemia-reperfusion injury in an experimental model. II. Renalase is involved in dopamine regulation in renal tubular cells and primary urine by means of (1) inhibition of LAT1 and depletion of tubular L-DOPA and the resultant reduction of dopamine synthesis and (2) degradation of dopamine and other catecholamines into inactive aminochromes. Renalase causes a reduction of natriuresis and phosphaturia by reducing the dopamine level and its inhibitory effect on Na^+/H^+ cotransporter and $Na^+/phosphate$ symporter. Renalase exerts an antiapoptotic action on renal tubular cells irrespective of its peptidase activity. DA = Dopamine; D_1R/D_5R = dopamine receptor type 1/5; DVR = direct vasa recta; IR = ischemia-reperfusion; PKC = protein kinase C; ↓ = decrease.

catecholamines (e.g. homovanillic acid) [37]. It has been documented that reninase production, plasma concentration and activity are largely dependent on the current level of catecholamines [38] (fig. 1). Based on the model of partially nephrectomized rats (excision of five sixths of the kidney tissue), the infusion of epinephrine, norepinephrine and dopamine with target blood pressure elevations of 15–20 mm Hg led to a nearly 3-fold increase in both plasma reninase concentrations and, most importantly, a 47-fold elevation of plasma reninase activity within 30 s, maintained for 60 min [38]. Remarkably, baseline reninase activity was minimal, suggesting that catecholamine excess may suppress reninase inhibitors or presumably transform proreninase into enzymatically active reninase [39]. In turn, plasma and renal tissue reninase contents were reduced by dietary sodium [40] and phosphate intake [41]. In animal models, reninase knockout mice were prone to higher blood pressure levels, tachycardia and hypophosphatemia and suffered a 3-fold greater extent of ischemic

myocardial damage than wild-type mice [42]. In turn, the administration of recombinant renalase completely protected against the induced myocardial ischemia [42]. Recombinant renalase administration significantly lowered catecholamine levels and blood pressure, while single nucleotide polymorphisms of the renalase gene were linked to a less pronounced hypotensive effect of renalase on the strength of decreased catalytic properties [37]. In a different 5/6 nephrectomy rat model, prolonged 4-week daily subcutaneous renalase injections caused a significant reduction of mean arterial pressure, left ventricular mass-to-body weight ratio and myocardial fibrosis as reflected in the left ventricular hydroxyproline concentration [43]. Thus, renalase has the potential to become a powerful hypotensive drug in the future [44]. On the basis of a rat model, surgical renal artery denervation led to an initial increase in renalase consistent with lower blood pressure 1 week after the procedure ($p < 0.05$), followed by a further renalase reduction and blood pressure elevation during 6 weeks of observation [45].

In human studies, renalase was shown to be inversely correlated with systolic blood pressure in a subset of patients with resistant hypertension [46]. Furthermore, various polymorphisms of renalase were significantly associated with a higher prevalence of primary arterial hypertension [47], myocardial hypertrophy, left ventricular systolic and diastolic dysfunction, impaired exercise tolerance [17], stroke and diabetes type 1 [48].

Renalase and Renal Function

Interestingly, renal function and the amount of functional residual renal mass are the crucial discriminators of renalase concentration [49]. Renalase participates in renal tubular and urinary catecholamine turnover. Not only is it secreted by proximal tubular and glomerular cells, but it also has a profound impact on the regulation of plasma sodium and phosphate levels.

Under basal conditions, renalase metabolizes dopamine in primary urine, preventing its impact on D_1 receptor [50] and thereby limiting the inhibitory effect of D_1 receptor stimulation on sodium-proton exchanger [51], sodium-phosphate co-transporter [41] and L-type amino acid transporter 1 (LAT1) [51]. In renalase-deficient mice, an increased renal dopamine output was linked to increased dopamine synthesis via overexpression of LAT1, leading to greater L-DOPA availability rather than reduced metabolism of dopamine [51]. A reduction of renalase leads to excess natriuresis and phosphaturia [41] (fig. 1).

As the kidney is the main site of renalase synthesis, it was noted that the CKD rat model (3/4 nephrectomy) was associated with low plasma renalase levels, partially compensated by a rise in plasma renalase activity [39]. Of note, this was initially demonstrated in humans with end-stage renal disease [16]. A high-sodium diet further exacerbated the discrepancy between markedly reduced renalase concentrations in CKD rats and those in controls, suggesting that impaired renalase expression in CKD might contribute to higher blood pressure values and increased cardiovascular risk [39]. This could partially explain the sympathetic overactivity and high prevalence of arterial hypertension among patients with CKD [52]. In the study performed at our institute covering adult patients long after successful repair of aortic coarctation, renalase was inversely correlated with SCr [53]. Conversely, a series of studies conducted by the group directed by Małyszko [54, 55] implied a stepped elevation of plasma renalase with the progression of CKD, as well as among kidney allograft recipients, which requires clarification in future studies.

At the same time, urinary renalase was shown to be independent of functional kidney mass [39]. However, in the setting of acute renal ischemia, urinary renalase levels temporarily decreased within the first hour after the ischemic event and subsequently returned to baseline levels [56]. In the event of global prolonged renal ischemia, the reduction in urinary renalase

concentration was profound and prolonged [56], which might indicate the potential use of urinary renalase as a marker of AKI (fig. 1). Accordingly, Lee et al. [57] confirmed the selective expression of renalase in proximal tubular cells and demonstrated a 2-fold increase in plasma catecholamines in renalase knockout mice, further potentiated by renal ischemia. In addition, renalase-depleted mice suffered greater ischemia-reperfusion renal injury as reflected in higher SCr and a greater extent of histologically assessed proximal tubular necrosis, apoptosis and inflammation in comparison to renalase wild-type specimens subjected to comparable ischemic insult [57]. Renalase pretreatment both 10 min before and 30 min after renal ischemia hampered the creatinine and catecholamine surge, and limited the extent of tubular necrosis, as well as neutrophil and macrophage infiltration [57]. Renalase was also documented to alleviate cisplatin-induced AKI independently of amine oxidase activity and catecholamine turnover, suggesting an effect on intracellular signaling cascades [58].

Most importantly, a recent study incorporating a rat model of ioversol-induced CI-AKI found a notable protective impact of renalase pretreatment on renal morphology and function [59]. A single intraperitoneal dose of recombinant renalase (2 mg/kg) administered 30 min before CM exposure considerably alleviated the SCr ($p < 0.05$) and blood urea nitrogen surge, and reduced renal tubular necrosis as reflected in the lower histopathological score, in comparison to ioversol with placebo. The clinical benefit of renalase was multifaceted, since renalase decreased the intrarenal inflammatory response, reduced tubular apoptosis (with a lower amount of TUNEL-positive cells and reduced caspase-3 activity) and blunted contrast-induced oxidative stress as reflected in the lower levels of cell membrane lipid peroxidation end products and the higher availability of superoxide dismutase as compared to rats exposed to ioversol alone. Renalase was also linked to renal cytoprotection based on an in vitro model of HK-2 cells [59].

Further research is warranted to confirm the possible role of renalase in CI-AKI, as it interferes with both ischemic and cytotoxic mechanisms involved in CI-AKI pathophysiology (fig. 1). Unfortunately, no randomized controlled trial has yet investigated into the possible role of renalase as a marker of AKI. Presumably, plasma renalase deficiency and catecholamine excess could contribute to medullary hypoxia shifting the balance towards direct vasa recta constriction, while intrarenal renalase suppression could aggravate apoptosis and necrosis and contribute to the well-described natriuresis following CM administration. Plasma renalase concentration could serve as a marker of vulnerability to renal injury, while exogenous recombinant renalase administration could serve as a preventive and therapeutic agent in contrast-induced nephropathy [56, 57, 59].

Conclusions

High hopes are placed on novel CI-AKI biomarkers, including renalase. This catecholamine-metabolizing enzyme could facilitate not only the early diagnosis of CI-AKI but also the stratification of patients according to the cardiovascular risk inherent in contrast-induced nephropathy. Future renal function indices should reflect not only the extent of kidney injury but also the magnitude of the combined cardiorenal pathology.

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