Midkine as a novel biomarker for contrast-induced acute kidney injury

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ABSTRACT

Contrast-induced acute kidney injury (CI-AKI) is an intrinsic kidney injury caused by contrast injection in susceptible individuals. Although the pathophysiological mechanisms by which contrast agents induce kidney injury have not been completely explained, direct and indirect effects, as well as hemodynamic perturbations, have been suggested. Renal effects develop immediately after contrast injection, and, theoretically, they could be detected early by using a sensitive biomarker. Recently, studies have been conducted to determine specific biomarkers to guide the early diagnosis of CI-AKI and thus improve the outcomes of these patients. Midkine (MK) is a heparin-binding growth factor that balances cell growth, survival, and migration. It has an antiapoptotic activity in nephrogenesis. Midkine has been investigated as an early biomarker for CI-AKI in patients undergoing percutaneous coronary intervention (PCI) for stable angina and was significantly higher in CI-AKI patients post PCU. However, more studies are needed to validate its efficacy in the early detection of CI-AKI.

Keywords: Contrast-induced nephropathy, contrast-induced acute kidney injury, midkine, biomarker.

BACKGROUND

Contrast-induced acute kidney injury (CI-AKI) accounts for one-third of all hospital-acquired acute kidney injuries (AKI) with an incidence of 1–2% in the general hospitalized population and up to 50% in high-risk individuals.[1] Contrast-induced acute kidney injury is defined as AKI that develops within 24–48 hours after exposure to contrast media and exclusion of other causes.[2] Contrast-induced acute kidney injury can be diagnosed if there is a 25% relative increase or a 0.5 mg/dl absolute rise in serum creatinine (SCr) level within 72 hours after contrast exposure with no other alternative explanation.[1] Certain limitations in the diagnostic criteria exist, including the absence of functional assessment, such as changes in urine output, which is used in the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE),[3] Acute Kidney Injury Network (AKIN),[4] and Kidney Disease Improving Global Outcomes (KDIGO)[5] classifications. A slight increase in SCr, less than 0.5 mg/dl, was also found to correlate with adverse events.[2] Nevertheless, this definition is widely used in most CI-AKI studies, and it correlates well with adverse clinical endpoints.[6]

Given the progressive reduction in hospital length of stay for diagnostic and interventional procedures, detection of CI-AKI in this setting will continue to be challenging. In addition, emerging evidence suggests that SCr lacks the sensitivity to diagnose occult but clinically relevant AKI,[7] and increased SCr levels provide no information regarding the etiology or anatomical location of renal injury.[8] Since the clinical manifestations and treatment of CI-AKI are, in fact, the same as AKI induced by other causes, the biomarkers studied to make a rapid diagnosis of AKI-induced by other causes

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could also be used to predict CI-AKI.[9] For these reasons, studies to identify and validate novel biomarkers with higher sensitivity for early CI-AKI are important.

Midkine (MK) is a heparin-binding growth factor that has a role in organogenesis and several pathologic conditions; it belongs to the pleiotrophin/MK family.[10] Human MK is a 13 kDa protein with 121 amino acids.[10] Despite abundant expression of MK during embryogenesis, evidence suggests that, during adulthood, MK is expressed only in certain organs, including the kidneys, intestines, and bronchial epithelium.[10] Midkine is involved in many physiological processes, such as growth and differentiation, reproduction, and tissue repair.[11] Midkine is also involved in inflammation, as is evident in *in-vivo* models of arterial restenosis, rheumatoid arthritis, ischemic renal injury, cisplatin-induced tubulointerstitial nephropathy, and diabetic nephropathy.[12] The expression of MK is reportedly upregulated following ischemic injury in various organs.[10] In the healthy kidney, MK is expressed in the glomeruli, interstitium, proximal and distal tubular cells, and endothelial cells.[11] However, the expression of MK is markedly upregulated in the epithelium of the proximal tubules, through the activation of hypoxia-inducible factor-1α (HIF-1α) during oxidative stress.[13] In this mini-review, we have summarized the evidence suggesting a role for MK in renal disease and suggest that MK could be an early indicator for diagnosing CI-AKI.

Midkine expression in nephrogenesis

During the mid-gestational period of embryogenesis, MK is abundantly expressed in metanephrogenic blastema due to modulation by retinoic acids. The growth of the embryonic kidney depends on mesenchymal-epithelial interactions. It has been proposed that MK is implicated in the development of renal epithelial tissues, since *in-vitro* inhibition of MK led to a decrease in the formation of nephrons by approximately 50%.[14]

Midkine in renal disease

The pathophysiological effects of MK in renal disease are diverse, varying from the development of acute kidney injury (AKI) to chronic kidney disease (CKD) progression, and it is also involved in renal ischemia and diabetic nephropathy.[15] Several mechanisms have been proposed as the underlying pathophysiology of MK-associated chronic kidney disease, including inflammatory cell infiltration through chemokines and progressive fibrosis due to the activation of transforming growth factor beta-1.[16] From a study of 197 patients with pre-dialysis CKD, the levels of serum and urine MK significantly increased in a step-wise manner across CKD stage III-V,[16] which may be explained by reduced renal excretion, increased renal production from damaged tubules, or chronic inflammatory state from CKD itself.[16] In this study, the median serum level of MK in normal volunteers was 754 pg/ml. There was a positive correlation between the level of MK and the severity of CKD. The reported mean serum level of MK was as high as 4816 pg/ml in CKD-V patients.[16] Limited evidence exists regarding the implication of MK in dialysis patients, but it was shown that the administration of heparin, but not non-heparin anticoagulants, in those patients resulted in a rapid elevation of the serum MK levels.[16]

Diabetic nephropathy is one of the most frequent causes of morbidity and mortality in diabetic patients. Long-standing hyperglycemia induces severe endothelial dysfunction, oxidative stress, and inflammation, leading to renal dysfunction.[14] It has been shown that the levels of MK are markedly elevated in children with type 1 diabetes mellitus, particularly in those with albuminuria.[17]

Renal ischemia is associated with systemic involvement and can lead to multiorgan failure.[18] During renal ischemia, energy depletion in renal epithelial cells results in cytoskeletal disruption, aberrant cell polarity, and cellular death.[18] In addition, indirect injury can be explained by the MK-mediated upregulation of macrophage inflammatory protein-2 (MIP-2) and subsequent recruitment of inflammatory cells.[18] A previous study showed that extreme ATP and GTP consumption is associated with necrotic and apoptotic cell death, respectively.[19] Endothelial cell malfunction causes vascular congestion and edema, blood flow impairment, and the migration of inflammatory cells, such as neutrophils and macrophages to the injured kidney followed

by a release of cytokines, reactive oxygen species, proteases, myeloperoxidase, and other chemokines to cause additional damage.[18] Following renal ischemic/reperfusion injury, it has been shown that the synthesis of MK is significantly increased in diseased tubules, which is associated with elevated levels of MIP-2.[20] Inhibiting both MK and MIP2 results in decreased infiltration of neutrophils and macrophages, thus reducing the intensity of tubulointerstitial injury.[18,20]

Using MK as a renal biomarker in CI-AKI has been studied in patients with stable angina undergoing percutaneous coronary intervention (PCI). It was demonstrated that the serum levels of MK were significantly higher in CI-AKI patients.[21] An increase in serum MK was detected as early as 2 hours following PCI, with the mean serum levels of 2,460 pg/ml, and it remained significantly elevated for 8 hours after the procedure.[21] Ahmed et al.[22] studied the use of serum MK as an early predictor of CI-AKI in 100 patients with eGFR < 60 ml/min/1.73 m^2 undergoing PCI for the acute coronary syndrome (ACS). Serum MK levels were measured before PCI and 2 and 24 hours after PCI. The results showed that the serum levels of MK at 2 hours post-PCI can be used as an early predictor of CI-AKI in ACS patients undergoing PCI. Jones et al. stated that MK might be more sensitive in AKI diagnoses than other biomarkers. Comparing MK measurement with other biomarkers can increase the sensitivity for AKI diagnosis.[23] Nevertheless, more studies are necessary to validate using MK in CI-AKI.

Conclusion

Overall, the pathogenesis of CI-AKI is not yet completely understood. Although often a brief injury, CI-AKI may progress to significant persistent renal impairment, end-stage kidney disease, and adverse cardiovascular sequelae. Current studies are largely focused on CI-AKI prevention in susceptible patients. However, no consensus regarding the treatment of CI-AKI has been developed once it occurs. In current clinical practice, SCr and assessment of urine output are the most commonly used measures of renal dysfunction, but they have limited sensitivity and specificity. Serum creatinine is a marker of function, not injury, and it may take days after injury to increase, thereby limiting its usefulness in the early detection of CI-AKI. It is possible that the renal injury starts immediately after contrast administration. Sensitive early biomarkers may be able to detect kidney injury promptly, and to this effect, much effort has been made in recent years to identify the appropriate marker. The development of novel biomarkers, such as MK, is promising and may provide more rapid detection of CI-AKI before the expected rise in SCr and give a diagnosis in hours, rather than days, which could lead to improved patient outcomes.

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