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Hepcidin – Potential biomarker of contrast-induced acute kidney injury in patients undergoing percutaneous coronary interventions

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ABSTRACT

Purpose: Contrast-induced acute kidney injury (CI-AKI) is a common and potentially serious complication of percutaneous coronary interventions (PCI). In this study, we tested the hypothesis whether serum and urinary hepcidin could represent early biomarkers of CI-AKI in patients with normal serum creatinine undergoing PCI. In addition, we assessed serum and urinary neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, eGFR and serum creatinine in these patients.

Methods: Serum and urinary hepcidin and NGAL, serum cystatin C, were evaluated before, and after 2, 4, 8, 24 and 48 h after PCI using commercially available kits. Serum creatinine was assessed before, 24 and 48 h after PCI.

Results: We found a significant rise in serum hepcidin as early as after 4 and 8 h when compared to the baseline values. Serum NGAL increased after 2, 4 and 8 h, and in urinary NGAL after 4, 8 and 24 h after PCI. We found a significant fall in urinary hepcidin after 8 and 24 h after PCI. Serum cystatin C increased significantly 8 h after PCI, reaching peak 24 h after PCI and then decreased after 48 h. The prevalence of CI-AKI was 8%. Urine hepcidin was significantly lower 8 and 24 h after PCI in patients with CI-AKI, while serum and urine NGAL were significantly higher in patients with CI-AKI.

Conclusions: Our findings suggest that serum hepcidin might be an early predictive biomarker of ruling out CI-AKI after PCI, thereby contributing to early patient risk stratification. However, our data needs to be validated in large cohorts with various stages of CKD.

1. Introduction

In current clinical practice, acute kidney injury (AKI) is typically diagnosed by measuring serum creatinine in timely intervals. However, as it was shown in human and animal studies that steady state is reached within days after the insult. The loss of kidney function in AKI is most easily detected by measurement of the serum creatinine, which is also used to estimate the glomerular filtration rate (GFR) making eGFR useless in diagnosis and prognosis of AKI. Unfortunately, creatinine is an unreliable indicator during acute changes in kidney function [1]. First, using serum creatinine to estimate true renal function has well-recognized inaccuracies and limitations [2]. Unfortunately, conventional markers of AKI, such as serum creatinine, serum urea and urine output, lack diagnostic sensitivity and specificity and often identify patients with AKI only 24 or 48 h after surgery [3–5]. Accordingly, progress in this field is likely to depend, at least in part, on the availability of novel biomarkers for early and reliable diagnosis of AKI [6]. Over the past decade a number of early markers of AKI have been identified using genomic [7,8], proteomic [9] and laboratory methods. These biomarkers may prove useful in the early identification of patients at risk [4,5]. More recently, interest has focused on hepcidin as a regulator of iron homeostasis [10]. The hepcidin gene is regulated by iron loading, hypoxia or inflammation [10–12], and its protein is produced by liver and kidney cells [13]. In a pilot study of a nested cohort of 22 patients with AKI and 22 without AKI, Ho et al. [14] reported a greater postoperative signal/noise ratio for urine hepcidin levels in those patients who did not go on to develop AKI, suggesting that hepcidin may be the first clinically useful negative biomarker for

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AKI after cardiopulmonary bypass (CPB). Accordingly, we investigated the association of urine and serum hepcidin levels in patients undergoing cardiac surgery with the use of CPB. We aimed to (1) assess the predictive value of early postoperative urine hepcidin and serum hepcidin for ruling out AKI, (2) investigate the role of chronic kidney disease (CKD) on the predictive value of hepcidin and (3) explore whether changes in urine hepcidin reflect changes in serum hepcidin.

2. Patients and methods

The study was performed on 89 consecutive patients undergoing elective percutaneous coronary interventions (PCI) due to stable angina (II/III CCS class). We excluded patients with preexisting chronic kidney disease (more than 1.5 mg/dL in males and less than 1.2 mg/dL in females) and chose a population with normal serum creatinine, since in patients with impaired renal function we are aware of contrast induced nephropathy (CIN). None of the patients investigated had received nephrotoxic drugs at least 1 week before and during the study period. In all the patients 24 h before PCI all the nephrotoxic drugs (NSAIDs, diuretics, biguanidine derivatives in diabetic patients) were withdrawn and angiotensin converting enzyme (ACE) inhibitors were either withdrawn (when blood pressure permitted) or halved 24 h before the procedure. All the patients admitted to the Department of Invasive Cardiology (Bialystok, Poland) were recommended to drink about 2 liters of still water within 24 h periprocedurally.

Low-osmolal contrast agent was used in all the patients (iodixanol). All the patients were on statins and ACE inhibitors. Serum hepcidin, serum and urinary neutrophil gelatinase-associated lipocalin (NGAL) as well as cystatin C were evaluated before, and after 2, 4, 8, 24 and 48 h after PCI. Serum creatinine and urea were assessed before PCI, 24 and 48 h after the procedure. Hemoglobin, hematocrit, uric acid, cholesterol, HDL, triglycerides, fasting glucose, ejection fraction and left ventricular internal end-diastolic dimension (LVIDd), were studied at admission. Serum creatinine was measured by the standard laboratory method (Jaffe) in one central laboratory at the Medical University of Bialystok Clinical Hospital (Poland). We assessed kidney function according to CKD-EPI formula [15] and Cockcroft-Gault formula [16]. NGAL was evaluated using commercially available ELISA from ANTIBODYSHOP (Gentofte, Denmark). All tests were performed according to manufactures' instructions by the same person. Serum and urinary hepcidin was measured using commercially available kits from Bachem, UK.

2.1. Ethical issues

All the patients were informed about the aim of the study and gave their consent, the protocol was approved by the local Ethics Committee at the Medical University of Bialystok, Poland (approval number: R-I-002/331/2017).

2.2. Statistical analysis

Data given were analyzed using Statistica 13.1. ANOVA or Kruskal-Wallis ANOVA for repeated measurements with $p < 0.05$ considered statistically significant, when appropriate. Multiple regression analysis was used to determine independent factors affecting the dependent variable.

3. Results

Clinical and biochemical characteristics of the population studies is presented in Table 1.

We found a significant rise in serum hepcidin as early as after 4 h when compared to the baseline values (Fig. 1). It was also significantly higher 8 h after PCI. Serum NGAL increased after 2, 4 and 8 h, and urinary NGAL after 4, 8 and 24 h after PCI (Fig. 2). We found a significant fall in urinary hepcidin after 8 and 24 h after PCI. Serum cystatin C increased significantly 8 h, reaching peak 24 h after PCI and then decreased after 48 h (Table 2). When contrast nephropathy was defined as an increase in serum creatinine by > 25% of the baseline level 48 h after PCI, the prevalence of contrast-induced acute kidney

Table 1
Basal clinical characteristics of patients undergoing elective PCI.

parameters	
age (years)	60.67 ± 9.49
BMI (kg/m^2)	25.03 ± 6.54
SBP (mm Hg)	129.61 ± 47.50
DBP (mm Hg)	77.00 ± 27.81
Hemoglobin (g.dL)	14.31 ± 1.26
Albumin (g/L)	3.99 ± 0.81
Urea (mg/dL)	40.43 ± 19.98
Creatinine (mg/dL)	1.09 ± 0.24
Cockcroft–Gault formula (ml/min)	63.60 ± 28.88
Cockcroft–Gault formula adjusted for body mass (ml/min)	71.23 ± 21.78
CKD-EPI equation (ml/min/1.73 m^2)	85.45 ± 23.67
Cholesterol (mg/dl)	173.48 ± 47.02
HDL (mg/dl)	44.46 ± 10.13
triglycerides (mg/dl)	194.72 ± 81.07
Uric acid (mg/dL)	5.67 ± 1.51
fasting glucose (mg/dL)	122.12 ± 43.99
Ejection fraction (%)	49.12 ± 11.88
LVIDd-left ventricular internal enddiastolic dimension (cm)	5.36 ± 0.89
Duration of PCI (mins)	54.74 ± 26.58
Contrast volume (ml)	148.86 ± 94.64
Hypertension	28%
Diabetes	72%
Current smoker	4%
Past smoker	64%

Data given are means ± SD or percentage.

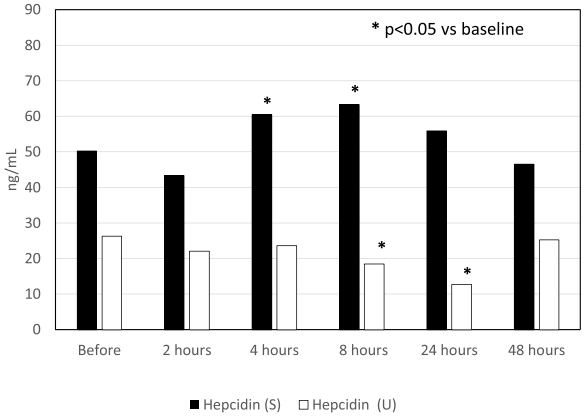

Fig. 1. Hepcidin changes in patients undergoing PCI.

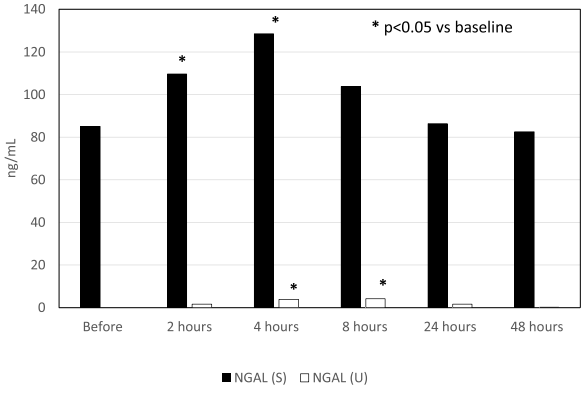

Fig. 2. NGAL changes in patients undergoing PCI.

Table 2
Kidney function assessed serum creatinine and cystatin C in patients undergoing PCI.

	Before coronary angiography	2 h	4 h	8 h	24 h	48 h
Cystatin C (mg/L)	1.55 ± 1.06	1.69 ± 1.07	2.09 ± 1.17	1.99 ± 1.26	2.59 ± 1.05-**	1.80 ± 1.07
Creatinine (mg/dL)	1.09 ± 0.24	ND	ND	ND	1.04 ± 0.32	1.08 ± 0.21

Data given are means ± SD.
ND – not done.
** $p < 0.01$ vs baseline.

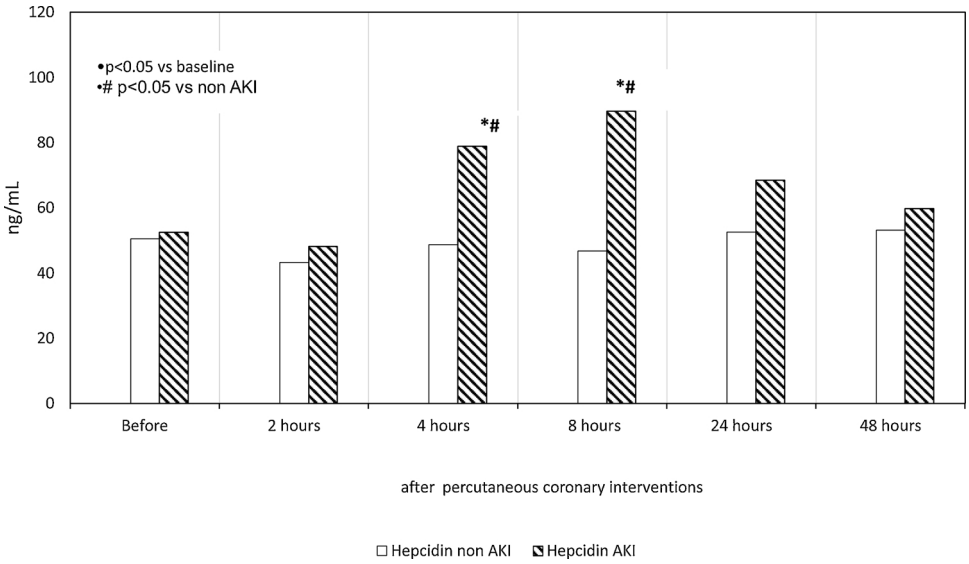

Fig. 3. Serum and urinary hepcidin in patients with AKI and not developing AKI.

injury (CI-AKI) was 8%. Urine hepcidin was significantly lower 8 and 24 h after PCI in patients with CI-AKI (Fig. 3), while serum and urine NGAL were significantly higher in patients with CI-AKI. NGAL levels were significantly higher in patients with CI-AKI starting 2 h after PCI (serum NGAL) or 4 h (urinary NGAL) when compared to patients without CI-AKI. Serum hepcidin correlated negatively with NGAL ($r = -0.42$, $p < 0.05$).

In multivariate analysis there were no predictors of serum or urinary hepcidin.

4. Discussion

Urinary hepcidin-25 was evaluated as a diagnostic biomarker of AKI in adult cardiac surgery cohorts [17–19]. However, there are no data available on hepcidin levels undergoing PCI. In a prospective nested-case-control study of individuals undergoing CPB surgery, Ho et al. [14] reported that in a proteomic analysis of urine of individuals who did not develop AKI postoperatively two high-intensity peaks were present. One of these peaks was determined to be hepcidin-25. In a subsequent study using an ELISA kit to validate their earlier proteomic findings quantitatively, Ho et al. [17] reported that urinary hepcidin-25 was significantly elevated in patients with versus without AKI. Few years later, Choi et al. [20] found that urinary hepcidin-25 is elevated following cardiac surgery in AKI and non-AKI patients. Elevated urinary hepcidin-25 concentration was inversely associated with AKI on both univariate and multivariate analyses. In the previous study by Ho et al. [17] hepcidin-25 was identified as a marker for AKI. In the recent study Choi et al. [20] also demonstrated that it was inversely associated with AKI at the first postoperative day. Their data corroborated with the study by Haase-Fielitz et al. [21]. Choi et al. [20] provided support for the utility of hepcidin as an early predictive biomarker of ruling out AKI by demonstrating that higher urinary hepcidin after CPB discriminates patients who do not develop AKI or do not need renal replacement therapy. These studies, in which hepcidin (which helps to sequester iron) is associated with protection, lend additional support for the role of catalytic iron in AKI. In our previous study, we found a significant rise in serum NGAL levels and in urinary NGAL after a PCI procedure [22]. The prevalence of CIN was 11%. In multivariate analysis, only serum creatinine was a predictor of serum NGAL before a PCI. NGAL may represent a sensitive early biomarker of renal impairment after PCI. In the present study, we confirmed the previous findings and extended the study using hepcidin as a novel potential biomarker of AKI in patients undergoing PCI.

In the experimental model of CI-AKI Hanss et al. [23] assessed the effect of an iron chelator on renal function. Rabbits pretreated with an iron chelator showed significant protection against a contrast-induced decrease in creatinine clearance, suggesting an important role of catalytic iron in this model. However, one should be cautious in extrapolating results from animal studies to humans because clinical trials in AKI based on animal models (e.g., anti-natriuretic peptide and IGF) have failed [24–27]. Nonetheless, evidence that catalytic iron seems to be involved in a variety of models of AKI suggests that this may be a common mechanism of tissue injury, and limited data from human studies [14,17,20] support this notion. Hepcidin is a major regulator of iron homeostasis that acts by binding to ferroportin receptors (iron-exporting proteins), leading to intracellular iron sequestration [28–30]. We stressed that both NGAL and hepcidin were involved in iron metabolism [31]. Both proteins sequester iron, but by different mechanisms. NGAL is an innate antibacterial factor the same as hepcidin. NGAL binds siderophores, thereby preventing iron uptake by bacteria.

Elevated NGAL a few days after insult is a possible preventive or protective mechanism limiting renal injury. Hepcidin as an antibacterial defensin, prevents iron absorption from the gut and iron release from macrophages, leading to hypoferremia and anemia. It has been suggested that hepcidin may act via alternate pathways to prevent death of tubular epithelial cells in the kidney [32,33]. A key role in AKI-induced cell death appears to play ferroptosis [34,35]. Inhibition of ferroptosis has exerted a protective effect, beyond inhibition of necrosis and necroptosis, in experimental model ischemia-reperfusion form of AKI [36]. In addition, upregulation of heme-oxygenase by a complex of iron:NGAL:siderophore has been demonstrated to be also nephroprotective [37]. Mårtensson et al. [38] investigated the value of combining both urinary biomarkers - NGAL and hepcidin - to estimate the severity and progression of AKI in intensive care unit (ICU) patients. They studied both biomarkers within 48 h of ICU admission in patients with the systemic inflammatory response syndrome and early kidney dysfunction defined as oliguria for ≥2 h and/or a 25 μmol/L creatinine rise from baseline. They found that NGAL increased ($P = 0.03$) whereas hepcidin decreased ($P = 0.01$) with increasing AKI severity. Up to date this is the only study to evaluate simultaneously these two biomarkers in urine. We studied both biomarkers in urine and serum. We observed a similar pattern of changes in urinary hepcidin and NGAL, however, in serum hepcidin was elevated in CI-AKI. We have previously reviewed the possible relations between NGAL and hepcidin [31]. Kidneys are involved in iron metabolism as there is abundant expression of Nramp2(DCT1), ferrous iron transporting protein, in the proximal tubule and collecting ducts of the kidney [13]. Moreover, Nramp1 expressed in the neutrophils granules known to harbor NGAL and lactoferrin, is believed to reduce the availability of iron in the phagocytic vacuoles by pumping iron into the cytosol. NGAL also binds small-iron carrying molecules - so called siderophores, critical in various states including bacterial infection and kidney injury [39–41]. In addition, distal nephron-urinary NGAL, synthesized in AKI and CKD, acts as a prophylactic antimicrobial agent [42]. NGAL was demonstrated to protect against acute ischemic kidney injury as it attenuates apoptosis of tubule cells and enhances tubular cell proliferation [36]. NGAL could potentially recycle iron into the viable cells, thus stimulating growth and development. By removing iron from the site of injury, NGAL may limit iron-mediated cytotoxicity. The rise in serum hepcidin in our present study may be due to the fact that hepcidin is produced by the liver and to some extent by renal tubular cells. Hepcidin is also upregulated during inflammation [37]. It leads to the intracellular iron sequestration and the attenuation of likely extracellular iron-induced damage. Thus, serum hepcidin may be elevated in AKI. The probable reason for lower urinary hepcidin in AKI could be either reduced tubular reabsorption or increased tubular delivery or both. Assuming, that tubular secretion of hepcidin significantly contributes to its urinary excretion, hepcidin consumption through binding and degradation of ferroportin might prevent intracellular hepcidin from entering the tubular lumen [43]. On the other hand, hepcidin has protective effects on iron-related cell death. Hepcidin may act as a chelator for reactive Fe [44,45]. Reduced renal tubular apoptosis was also observed in a mouse model of ischemia-reperfusion kidney injury after use of a hepcidin-inducing furin inhibitor [46]. In addition, iron deposition relates to oxidative cellular injury, as assessed by hemeoxygenase-1 staining [47], strengthens the supposition that iron accumulation facilitates highly reactive radical formation that damage membranes, proteins and DNA, and, subsequently, causes tissue injury [48]. As many of these stress pathways are intertwined it is difficult to determine the exact mechanism(s) involved, which may differ between locally synthesized and circulating hepcidin. In a comprehensive and thoughtful analysis of the various novel biomarkers that have been examined after CPB–associated AKI, Haase et al. [49] concluded that free iron–related kidney injury seems to be the unifying pathophysiologic connection for these biomarkers. Using biomarkers that are pathophysiologically linked to the disease process has major therapeutic implications [49]. The availability of iron chelators with favorable adverse effect profiles for short-term use makes them attractive for clinical trials aimed to prevent or treat AKI. In the recent study by Wang et al. [50], the authors measured urinary hemojuvelin (uHJV), kidney injury molecule-1 (uKIM-1), uNGAL, α-glutathione S-transferase (uα-GST) and π-glutathione S-transferase (uπ-GST) in urine. They found that the combination of this biomarker panel (normalized uKIM-1, uHJV at 3 h post-operation) and Liano's score was superior in predicting advanced AKI, however, there are some concerns about the assay they used for HJV determination. Therefore, the use of standardized assay is crucial [51]. It is also important to establish the normal range for the studied biomarkers [52].

The strength of our present study is a simultaneous measurement of NGAL and hepcidin, both involved in iron homeostasis. It provides a unique opportunity to study their interaction in patients undergoing PCI. We used commercially available assays and could compare our data with previously published studies. We would like to stress that our population is relatively homogeneous with low risk of AKI. Using our standard protocol, the prevalence of CI-AKI in our population was below 10%. We have also detailed clinical and demographic information on our patients to allow us to study the independent association of NGAL, hepcidin and the NGAL/hepcidin ratio with CI-AKI. On the other hand, we are fully aware of the limitations of our study. This is a single center study, in low-risk population, thus our findings may not be applicable to other patients.

5. Conclusions

Our findings suggest that serum hepcidin might be an early predictive biomarker of ruling out CI-AKI after PCI, thereby contributing to early patient risk stratification. However, our data needs to be validated in large patient cohorts with various stages of CKD.

Conflict of interests

The authors declare no conflict of interests.

Financial disclosure

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The author contribution

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Data Collection: Hanna Bachorzewska-Gajewska, Ewa Koc-Zorawska.

Statistical Analysis: Jolanta Malyszko, Hanna Bachorzewska-Gajewska.

Data Interpretation: Jolanta Malyszko, Joanna Matuszkiewicz-Rowinska, Jacek S. Malyszko, Hanna Bachorzewska-Gajewska, Slawomir Dobrzycki, Ewa Koc-Zorawska.

Manuscript Preparation: Jolanta Malyszko, Hanna Bachorzewska-Gajewska, Jacek S. Malyszko, Slawomir Dobrzycki.

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Funds Collection: Jolanta Malyszko, Hanna Bachorzewska-Gajewska, Slawomir Dobrzycki.

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