POTENTIAL BIOMARKERS OF CONTRAST-INDUCED ACUTE KIDNEY INJURY IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

Lavrishcheva Yu. V.[1], Konradi A. O.[1], Yakovenko A. A.[2]

[1]Almazov National Medical Research Centre, Saint Petersburg, Russia
[2]Academician I. P. Pavlov First Saint Petersburg State Medical University, Saint Petersburg, Russia

Corresponding author:
Lavrischeva Yulia V.,
Almazov National Medical Research Centre,
Akkuratova str. 2, Saint Petersburg,
Russia, 197341.
E-mail: lavrischeva@gmail.com

Received 04 October 2021; accepted 02 November 2021.

ABSTRACT

Currently, there is a continuous increase in the number of interventional interventions in cardiology using X-ray contrast agents (RKV), which often leads to such a formidable complication as contrast-induced acute kidney injury (CI-AKI). The manifestations of CI-AKI have all the characteristics of acute renal injury (AKI) and include an absolute (greater than or equal to 0.3 or more or equal to 0.5 mg/dL) or relative (greater than or equal to 25%) increases in serum creatinine (sCr) compared with baseline values, occurring 48-72 hours after intravascular administration of RVC.

Contrast-induced acute kidney injury is a common complication following intravascular administration of iodine-containing contrast media and is associated with prolonged hospital stay and poor long-term prognosis, including unwanted cardiovascular events, and complete loss of renal function. CI-AKI occurs in 5-20% of hospitalized patients undergoing percutaneous coronary interventions.

Unfortunately, there are currently no analogues of iodine-containing RVC, and therefore the question of finding optimal CI-AKI biomarkers for the purpose of early diagnosis and prevention of this formidable complication remains relevant.

The diagnosis of CI-AKI is based on an increase in serum creatinine, which is a late biomarker of kidney damage. New and earlier serum and urinary biomarkers for the diagnosis of kidney damage have now been identified that can be detected before serum creatinine levels rise. This article provides information on the most relevant and modern biomarkers of CI-AKI.

Key words: acute kidney injury, cardiovascular events, biomarkers, creatinine, percutaneous coronary interventions, X-ray contrast agents.

For citation: Lavrishcheva YuV, Konradi AO, Yakovenko AA. Potential biomarkers of contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention. Russian Journal for Personalized Medicine. 2021;1(1):173-191.

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) is a severe complication of exposure to radiopaque substances (ROS) used in cardiology for diagnosis or when using interventional treatment methods, and may be associated with unfavorable short- and long-term outcomes [1, 2]. CI-AKI is the third most common cause of nosocomial development of acute kidney injury (AKI) after reduced renal perfusion (within prerenal AKI) and drug nephrotoxicity. The incidence of CI-AKI varies up to 20% among hospitalized patients [2, 3]. CI-AKI is usually defined as an absolute (more than or equal to 0.3 or more than or equal to 0.5 mg/dl) or relative (more than or equal to 25%) increase in serum creatinine (sCr) compared to baseline values, occurring 48-72 hours after intravascular administration of ROS, and, reaching a peak on day 3-5, returns to the baseline level within 10-14 days [1]. Such dynamics of creatinine level does not allow timely diagnosis of CI-AKI. In addition, an increase in serum creatinine depends not only on a decrease in glomerular filtration rate (GFR), but also on the systemic accumulation of sCr produced by skeletal muscles and non-renal factors (age, gender, muscle mass, state of hydration), which makes an increase in sCr level non-specific for the diagnosis of CI-AKI, in connection with which other biomarkers have been actively investigated recently. In particular, there is a growing interest in the most sensitive biomarkers that allow detecting kidney injury earlier than the sCr level. These biomarkers can be divided into 2 groups: 1) those that represent changes in renal function [for example, sCr or cystatin (Cys-C)], 2) those that reflect structural kidney injury [for example, kidney injury molecule 1, interleukin-18 (IL-18)]. Several studies report new biomarkers in urine/serum used for risk stratification, diagnosis and prediction of the possibility of CI-AKI. The combination of functional biomarkers and biomarkers of kidney injury provides a simple method for dividing patients with AKI into 4 groups: 1) markers do not change; 2) only injury; 3) only functional disorders; 4) injury and functional disorders [4]. In fact, the use of new biomarkers of kidney injury has been limited for several reasons: finding the most accurate biomarkers for each individual case, uncertainty in thresholds (which may vary depending on the conditions), as well as limited clinical data and financial costs.

Characteristics of the optimal biomarker for detecting CI-AKI: 1) detection fluency and specificity for contrast-induced kidney injury; 2) cost-effectiveness; 3) the ability of detection at the subclinical phase; 4) the ability to monitor the biomarker; 5) the ability to stratify the risk and predict the outcome of kidney injury.

PATHOPHYSIOLOGY OF ACUTE KIDNEY INJURY INDUCED BY RADIOPAQUE SUBSTANCE

ROS can induce AKI by two main mechanisms: 1) cytotoxic effect; 2) impaired renal hemodynamics [5, 6]. Cytotoxic effects of ROS include: apoptosis, impaired cell viability and increased activity of the brush border and lysosomal enzymes; fragmentation of cellular DNA; suppression of signaling molecules involved in cell survival and amplification of signaling molecules during cell death, such as members of the N-terminal kinase p38 and c-Jun mitogen-activated protein kinases and nuclear transcription factor kB, as well as activation of caspase. It is believed that the nuclear factor kB and N-terminal kinases c-Jun are involved in enhancing the regulation of pro-inflammatory IL-8. The imbalance between vasoconstrictors and vasodilators is leading in the pathogenesis of CI-AKI.

In fact, haemodynamic compromise with an increase in renal blood flow, glomerular filtration rate and diuresis rate are directly related to the osmolality of ROS. Due to the increased osmotic load, more sodium is reabsorbed by tubular cells, which in itself increases oxygen consumption. After this temporary increase, the renal blood flow decreases (from 10 to 25%). The decrease in blood flow appears to occur under the influence of vasodilators, such as adenosine, nitric oxide, atrial natriuretic peptide and prostaglandin E2. Also, the pathogenesis of CI-AKI involves an increase in the production of reactive oxygen species due to a decrease in blood flow and increased oxygen consumption in the brain substance (Fig. 1).

FUNCTIONAL BIOMARKERS

Creatinine

Creatinine is the most widely used endogenous marker of glomerular filtration rate, produced at a constant rate and freely filtered in the glomeruli, with only 10 to 40% secreted by distal tubules. This is a convenient and cheap marker to measure, but its concentration is influenced by several factors, including age, gender, exercise, medication, muscle mass, nutritional status and number of meals [1].

The increase in sCr occurs 24-72 hours after the introduction of ROS and peaks on days 3-5, returning to the baseline level within 10-14 days. In addition to this slow kinetics which limits its use for early diagnosis of kidney injury, sCr remains within the reference range until 50% of renal function is lost.

Microalbuminuria

Microalbuminuria is an important marker of changes in the structure and function of the glomeruli. The term "microalbuminuria" refers to urinary albumin at a concentration below the threshold for determining albumin using conventional urine test strips. Its value ranges from 30 to 300 mg/l [7]. Microalbuminuria was used as a biomarker in a study of the prevention of CI-AKI with N-acetylcysteine [8]. The limitation of the use of microalbuminuria as a marker of AKI is its presence not only in acute, but also in chronic conditions, such as diabetes mellitus, blood diseases, chronic kidney disease, etc.

Cystatin C (Cys-C)

Cystatin C is a functional biomarker of glomerular filtration, more sensitive than sCr, for detecting acute (within 24 hours) changes in kidney function. It is a 13 kDa protein, a member of the cysteine protease inhibitor family, which is present in all nucleated cells. Cys-C is filtered by glomeruli and then metabolized in the cells of the proximal renal tubules after megalin-mediated endocytosis [9]. Cys-C is not secreted by the proximal renal tubules. All cells in the body that contain nuclei produce cystatin C at a stable rate. Thus, the concentration of cystatin C in the blood correlates with the glomerular filtration rate [10, 11]. The level of protein in the blood does not depend on body weight and height, muscle mass and gender.

For these reasons, Cys-C can be a useful marker for detecting both chronic and acute changes in GFR [12, 13]. In addition, Cys-C is distributed in the extracellular fluid, whereas sCr is distributed in the water of the whole body, the volume of which is 3 times larger

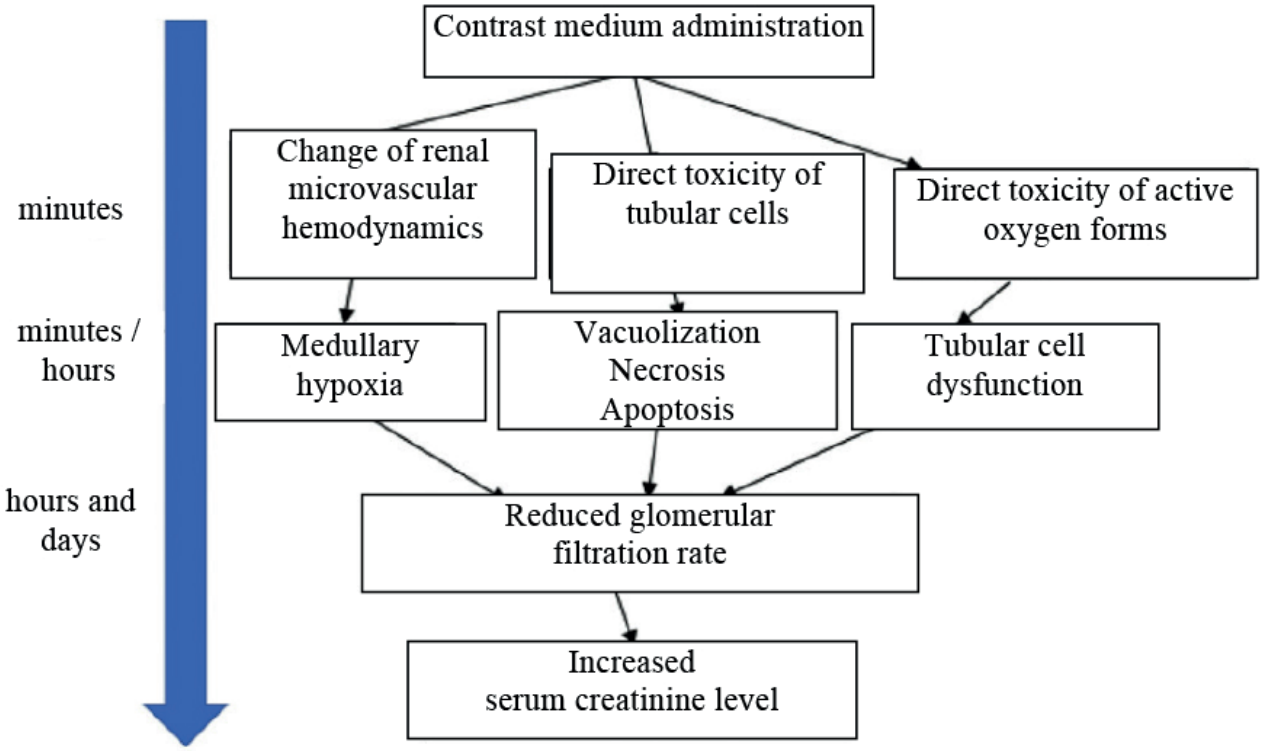

Fig. 1. Pathophysiology of acute kidney injury

[14, 15]. Thus, with a decrease in GFR, the content of Cys-C in serum increases faster than sCr [16, 17].

It has been shown that with CI-AKI, the peak level of Cys-C in blood serum is reached as early as 24 hours after the administration of ROS, which makes it possible to detect even minor changes in GFR [18-20].

Brigoori C. and colleagues demonstrated that in 410 patients with chronic kidney disease who underwent coronary and/or peripheral angiography and/or angioplasty, an increase in the concentration of Cys-C in serum by 10% or more 24 hours after exposure to ROS was associated with an increase in sCr greater than or equal to 0.3 mg/dl and was an independent predictor of serious consequences for 1 year, including death and renal replacement therapy (RRT). At the same time, an increase in the level of Cys-C in serum by less than 10% in 24 hours excluded CI-AKI [21].

Beta-2-microglobulin (B2M, B $_2$ M, Thymotaxin, Beta $_2$-Microglobulin).

Beta-2-microglobulin is an 11.8 kJ protein that is filtered by glomeruli and reabsorbed by the proximal tubules of the kidneys [22]. Although low levels of beta-2-microalbumin are found in the urine and serum of healthy people, after kidney injury its level increases due to a decrease in reabsorption by damaged tubules.

In particular, the baseline level of beta-2-microglobulin in serum is an important predictor of CI-AKI. Nozue and colleagues included 96 patients with stable angina who underwent routine percutaneous coronary intervention (PCI) [23].

They measured serum Cys-C and b2M, as well as fatty acid binding protein in the liver (FABP), b2M and N-acetyl-b-D-glucosamide (NAG) before and 1 day after PCI. In patients with CI-AKI (5%), baseline serum b2M and Cys-C levels were significantly higher than in patients without CI-AKI (4.2 ± 2.6 vs. 2.2 ± 1.0 mg/L, P = 0.0007 and (1.51 ± 0.52) vs. 1.11 ± 0.34 mg/L, P = 0.013, respectively).

The baseline level of b2M > 1.26 mg/dl showed 75% sensitivity and 80% specificity in predicting CI-AKI. Similar results were obtained by Li and his colleagues, who randomized 424 patients exposed to ROS [24].

CI-AKI was defined as an increase in SCr by 25% or higher or 0.5 mg/dL above baseline within 48 hours. Serum levels of b2M, Cys-C and creatinine were measured 0, 24 and 48 hours after coronary angiography.

Before using ROS, the risk of CI-AKI was predicted by both the baseline level of b2M and CysC. After the introduction of ROS, CI-AKI was determined by the level of B2m, Cys-C, creatinine and GFR. However, multivariate regression analysis confirmed that the baseline levels of B2m, Cys-C, creatinine and calculated GFR were independent predictors of CI-AKI.

Retinol-binding protein (RBP).

Retinol binding protein (RBP) is a 21 kDa protein that is filtered by the glomeruli and reabsorbed by the proximal tubules. It has been shown to be an adequate marker for the diagnosis of AKI; in particular, levels of RBP in urine before and after are used to assess the effectiveness of the prevention of AKI with N-acetylcysteine [25].

BIOMARKERS OF STRUCTURAL KIDNEY INJURY

N-acetyl-β-d-glucosamide (NAG)

N-acetyl-β-d-glucosamide (NAG) is a lysosomal enzyme (>130 kDa) that is produced by cells of the proximal tubules of the kidneys. In healthy people, NAG is present in the urine in small amounts. Damage to the renal tubule leads to an increase in its concentration in the urine due to the fact that it is not filtered by the glomeruli due to the large weight. However, elevated levels of NAG in the urine can also be the result of increased lysosomal activity without cell destruction [26].

Andreucci M. and colleagues included 590 patients who underwent coronary angiography for both stable and unstable coronary heart disease [27]. Urine samples of NAG, osmolality, and sCr were taken before and 1, 2, and 6 days after administration of low-osmolar nonionic ROS. CI-AKI occurred in 33 patients. In these patients, the levels of NAG and sCr in the urine on days 1 and 2 were significantly higher than at the baseline, and compared with patients without CI-AKI. NAG levels in the urine peaked earlier and grew much faster than sCr levels in patients with CI-AKI.

Lipocalin associated with neutrophil gelatinase (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein associated with human neutrophil gelatinase, which belongs to the lipopalin superfamily [28]. Monomeric (mainly) and heterodimeric forms are the predominant forms produced by tubules [29]. NGAL is filtered by the glomeruli and then reabsorbed by the proximal tubules, where it is partially cleaved by megalin and partially excreted in the urine. The concentration of NGAL in a healthy person is 20 ng/ml in both serum and urine. After damage to the cells of the renal tubules, NGAL is released into plasma and urine; this causes an increase in its concentration in plasma and urine much earlier than an increase in the concentration of sCr [30]. Thus, NGAL can be considered as a fairly informative and independent marker of AKI [31-33].

According to various sources, there is evidence of the potential role of NGAL as a reliable and prognostic marker of AKI, since its serum and urine levels rise

earlier than sCr. Some researchers say that the level of NGAL in plasma is less specific than its concentration in urine [34, 35].

Kidney Injury Molecule 1 (KIM-1)

Kidney injury molecule 1 (KIM-1), a type 1 transmembrane glycoprotein, is recognized as a potential biomarker for detecting ischemic or toxic damage to the proximal tubules [36, 37]. The extracellular domain KIM-1 is separated from the cell surface by a metalloproteinase-dependent process. This excretion with increased synthesis of KIM-1 is most likely the cause of increased release of KIM-1 in urine on the background of AKI [38, 39]. The use of urinary KIM-1 as a biomarker of AKI is based on the fact that in healthy people there is no expression of KIM-1 and its activation in the apical cell membrane of the tubules, as during AKI.

Liao B. and colleagues conducted a study that included 3,200 patients without chronic kidney disease (CKD) who underwent coronary angiography. CI-AKI was defined as an increase in serum creatinine by 0.3 mg/dl from the baseline level [40]. KIM-1 levels were measured before, as well as 6 and 48 hours after exposure to ROS [40]. The authors noticed that the levels of KIM-1 after 6 and 48 hours, compared with the baseline level, significantly increased in patients with CI-AKI, but not in the control group.

The role of KIM-1 as an early biomarker of CI-AKI was also confirmed in 145 patients with diabetes mellitus exposed to ROS [41]. In these patients, sCr levels were measured before administration of ROS and 24-48 hours after that. The urinary KIM-1 values were evaluated at the baseline level and within 2, 6, 12, 24 and 48 hours after the use of ROS. A total of 19 patients developed CI-AKI, which was diagnosed by the level of sCr. There was a significant difference between the levels of KIM-1 in urine measured 2, 6, 12, 24 hours after the procedure and the levels before the procedure in the CI-AKI group. There was no difference in the sCr level measured before and after 24 hours after the procedure. Not so long ago, Wybraniec M. T. and colleagues showed that urinary KIM-1 levels exceeding 0.425 ng/mL 6 hours after administration of ROS predicts with high sensitivity and specificity CI-AKI in patients undergoing coronary angiography [42].

Urinary interleukin-18 (IL-18)

IL-18 is a cytokine that increases in the proximal renal tubules in patients with AKI, and is formed from the IL-18 precursor under the action of caspase-1 [43]. Levels of IL-18 in urine increase with acute tubular necrosis, but not with prerenal AKI. It is a sensitive and specific biomarker of AKI [36]. A meta-analysis of 23 studies has demonstrated that IL-18 in urine is a reliable biomarker of AKI in patients who have undergone cardiac surgery, hospitalized in intensive care units and cardiology departments [44-48].

Fatty Acid Binding Protein, Liver Form (L-FABP)

The liver fatty acid binding protein (L-FABP) is expressed in the proximal tubules of the human kidney and participates in the metabolism of fatty acids [49]. There are two types of FABP found in the kidneys: L-FABP, located in the proximal convoluted and straight tubules of the kidneys (it can also be reabsorbed from the glomerular filtrate through megalin, multigand proximal tubular endocytic receptor), and cardiac-type FABP which is not found in the urine. Thus, only L-FABP has been approved as a biomarker of tubule injury. In the promoter region of the L-FABP gene, there is an element that reacts to hypoxia, and some studies have reported that the concentration of L-FABP in the urine increased in parallel with a decrease in peritubular blood flow, thus, L-FABP can be determined by changes in renal hemodynamics after administration of ROS. Some studies have shown that baseline levels of L-FABP in urine correlated with the occurrence of CI-AKI [50].

Hishikari K. and colleagues compared the levels of L-FABP in urine before and after coronary angiography in 66 patients with sCr from 1.2 to 2.5 mg/dl and in 30 volunteers [51]. Prior to angiography, L-FABP levels were significantly higher in 13 patients in whom subsequently sCr level increased and CI-AKI developed. In particular, Menez S. and colleagues found that urinary Cr level greater than or equal to 24.5 mg/g prior to exposure to ROS was an independent predictor of CI-AKI [52]. In addition, measuring changes in the level of L-FABP in urine before and 24 hours after cardiac catheterization in patients with mild to moderate renal dysfunction may be an important indicator of stratification of the risk of the onset of cardiovascular events [53].

Midkin (MK)

Midkin (MK) is a 13 kDa heparin-binding growth factor with various biological functions, such as migration of inflammatory cells and anti-apoptotic effect [54]. In the kidneys, MK is expressed both in the cells of the proximal tubules and in the epithelial cells of the distal tubules and to a lesser extent in endothelial cells and is induced by oxidative stress through the activation of factor 1-alpha caused by hypoxia [54]. The pathophysiological roles of MK vary, from the onset of AKI to the progression of CKD [55].

Malyszko J. and colleagues conducted a study aimed at clarifying whether MK could be an early biomarker of CI-AKI [56]. A total of 89 patients with nor-

mal sCr levels who had undergone PCI were examined. Serum MK was assessed at the baseline level and 2, 4, 8, 24 and 48 hours after administration of ROS; sCr was evaluated before and 24 and 48 hours after administration of ROS. CI-AKI was defined as an increase in sCr by more than 25% from the baseline level 48 hours after PCI and occurred in 10% of patients. In these patients with CI-AKI, a significant increase in serum MK level was observed 2 hours ($P < 0.0019$) and 4 hours after exposure to ROS; MK returned to the baseline value after 24 hours. In the same study, NGAL levels were significantly higher 2 hours (sNGAL) or 4 hours (uNGAL) after PCI. Cys-C was higher 8 and 24 hours after PCI in patients with CI-AKI.

Dickkopf-3 (DKK3)

A new biomarker for the diagnosis of progressive tubulointerstitial fibrosis. DKK3 belongs to the glycoprotein family (DKK1-4), which primarily modulate the Wnt signaling pathway. This signaling pathway is involved in various cell functions, such as proliferation, migration and gene expression of fibrogenic cytokines. A number of experimental studies has shown that the Wnt signaling pathway is also involved in the progression of chronic kidney disease [57]. DKK3 is released from "stressed" tubular cells in the urine. Thus, significant kidney injury is detected at an early stage. The disadvantage of this method may be that this method is eminently suitable as additional information for GFR, but is more relevant for patients with chronic kidney disease (Figure 2).

OTHER BIOMARKERS

· Protein 7 binding insulin-like growth factor and tissue metalloproteinase-2 inhibitor are 2 proteins involved in cell cycle arrest that can be predictors of AKI. Actually, cell cycle arrest may be the result of cell damage caused by ROS [54].

· Gamma-glutamyltranspeptidase (GGT) is an enzyme on the brush border of the proximal tubules of the kidneys, which appears in the urine when the brush border is damaged. Elevated baseline GGT levels can predict CI-AKI [34, 57].

MiRNA is a molecule involved in cell proliferation, differentiation and death, as well as in inflammation, which suggests their involvement in the pathogenesis of CI-AKI [58]. MiRNA molecules have the advantage of their stability in serum, urine and saliva.

CONCLUSIONS

CI-AKI is one of the most common causes after percutaneous coronary interventions, associated with prolonged hospital stay and adverse outcomes, including various adverse cardiovascular outcomes and loss of renal function up to the terminal stage. Given the continuous increase in the number of performed PCIs using ROS, the frequency of CI-OPP will continuously increase. There is also an increase in the number of comorbid patients with endocrinological pathology, chronic kidney disease, which also increases the risk of CI-AKI. Currently, in clinical practice, sCr is still wide-

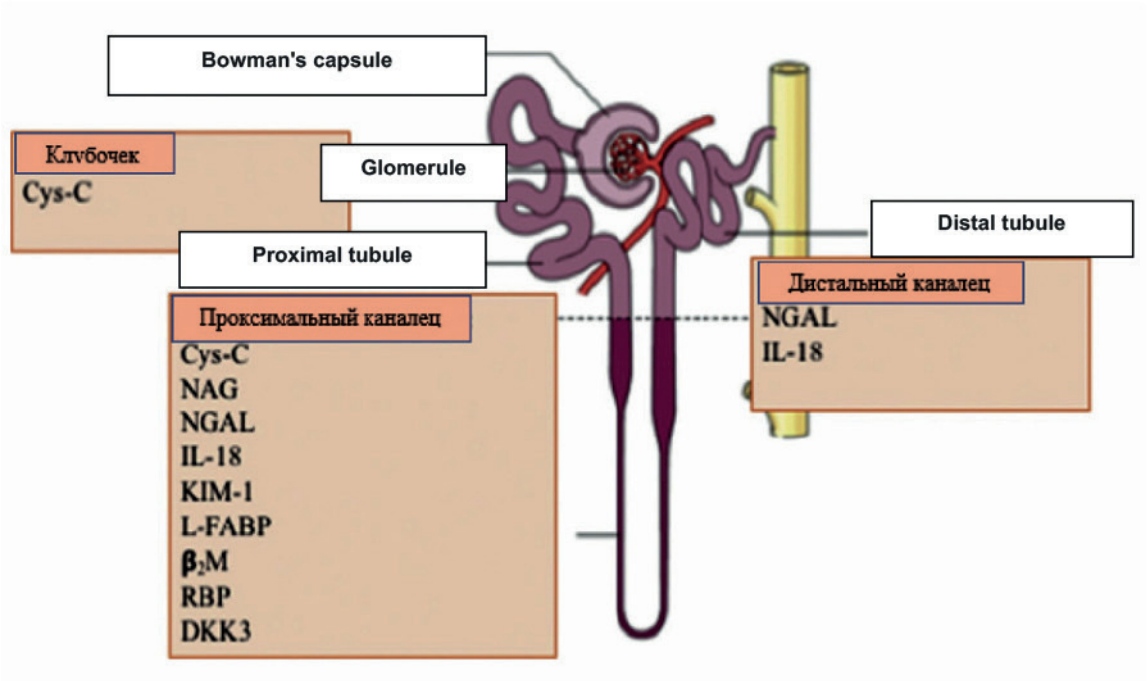

Fig. 2. Release of CI-AKI biomarkers in various parts of the nephron

ly used as a marker of kidney injury, despite the fact that its increase is delayed and its concentration may depend on age, increased muscle mass and concomitant therapy. In this regard, it became necessary to search for new early biomarkers of renal injury.

Recently, several promising biomarkers have been identified that presumably can be predictors of kidney injury in cardiac patients until sCr increases. The most promising markers of CI-AKI are Cys-C, NGAL, KI-1, IL-18 and L-FABP, as their use can help in the diagnosis of acute kidney injury in the subclinical phase of the disease. However, some questions remain unresolved regarding the accuracy and reliability of these new biomarkers in the context of contrast-induced nephropathy.

Preferably, an ideal biomarker should be non-invasive, detectable at an early stage of the disease, prognostically significant, and, most importantly, it should be specific for kidney injury when using ROS and have a pathophysiological correlation with the disease. Therefore, in order to find the ideal biomarker, it is necessary to conduct a multicenter clinical study to find out the potential of these biomarkers in different groups of patients.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Tehrani S, Laing C, Yellon DM, et al. Contrastinduced acute kidney injury following PCI. Eur J Clin Invest. 2013;43:483–90. DOI: 10.1111/eci.12061.
2. Santiago G, Byungsoo K, Selcuk A. Contrast-Induced Nephropathy and Risk of Acute Kidney Injury and Mortality After Cardiac Operations. The Annals of Thoracic Surgery. 2012;94(3):772–6. DOI: 10.1016/S0002-9343(97)00150-2.
3. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicentre study. JAMA. 2005;294(7):813–8. DOI: 10.1001/jama.294.7.813.
4. McCullough PA, Shaw AD, Haase M, et al. Diagnosis of acute kidney injury using functional and injury biomarkers: workgroup statements from the tenth acute dialysis quality initiative consensus conference. Contrib Nephrol. 2013;182:13–29. DOI: 10.1159/000349963.
5. D'Amore C, Nuzzo S, Briguori C. Biomarkers of Contrast-Induced Nephropathy: Which Ones are Clinically Important? Intervent Cardiol Clin. 2020;9:335–44. DOI: 10.1016/j.iccl.2020.02.004.
6. Heyman SN, Rosen S, Rosenberger C. Renal parenchymal hypoxia, hypoxia adaptation, and the pathogenesis of radiocontrast nephropathy. Clin J Am Soc Nephrol. 2008;3(1):288–96. DOI: 10.2215/CJN.02600607.
7. Ferguson MA, Vaidya VS, Bonventre JV. Biomarkers of nephrotoxic acute kidney injury. Toxicology. 2008;245:182–93. DOI: 10.1016/j.tox.2007.12.024.
8. Chousterman BG, Bouadma L, Moutereau S, et al. Prevention of contrast-induced nephropathy by N-acetylcysteine in critically ill patients: different definitions, different results. J Crit Care. 2013;28(5):701-9. DOI: 10.1016/j.jcrc.2013.03.007.
9. Weyer K, Nielsen R, Petersen SV, et al. Renal uptake of 99mTc-dimercaptosuccinic acid is dependent on normal proximal tubule receptor-mediated endocytosis. J Nucl Med. 2013;54(1):159-65. DOI: 10.2967/jnumed.112.110528.
10. Ghys LF, Meyer E, Paepe D, et al. Analytical validation of a human particle-enhanced nephelometric assay for cystatin C measurement in feline serum and urine. Vet Clin Pathol. 2014;43(2):226-34. DOI: 10.1111/vcp.12144.
11. Obiols J, Bargnoux AS, Kuster N, et al. Validation of a new standardized cystatin C turbidimetric assay: evaluation of the three novel CKD-EPI equations in hypertensive patients. Clin Biochem. 2013;46(15):1542-7. DOI: 10.1016/j.clinbiochem.2013.05.056.
12. Schaeffner E. Determining the Glomerular Filtration Rate-An Overview. J Ren Nutr. 2017;27(6):375-80. DOI: 10.1053/j.jrn.2017.07.005.
13. Gaygısız Ü, Aydoğdu M, Badoğlu M, et al. Can admission serum cystatin C level be an early marker subclinical acute kidney injury in critical care patients? Scand J Clin Lab Invest. 2016;76(2):143-50. DOI: 10.3109/00365513.2015.1126854.
14. Shams E, Mayrovitz HN. Contrast-Induced Nephropathy: A Review of Mechanisms and Risks. Cureus. 2021;13(5):e14842. DOI: 10.7759/cureus.14842.
15. He Y, Deng Y, Zhuang K, et al. Predictive value of cystatin C and neutrophil gelatinase-associated lipocalin in contrast-induced nephropathy: A meta-analysis. PLoS One. 2020;15(4):e0230934. DOI: 10.1371/journal.pone.0230934.
16. Wang ZY, Wang YL, Wei J, et al. Role of serum cystatin C in the prediction of contrast-induced nephropathy after intra-arterial interventions. Chin Med J (Engl). 2020;133(4):408-414. DOI: 10.1097/CM9.0000000000000641.
17. Briguori C, Quintavalle C, Donnarumma E, et al. Novel biomarkers for contrast-induced acute kidney injury. Biomed Res Int 2014;2014:568738. DOI: 10.1155/2014/568738.
18. Coppolino G, Comi N, Bolignano D, et al. Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) Predicts Renal Function Decline in Patients With Glomerular Diseases. Front Cell Dev Biol. 2020;8:336. DOI: 10.3389/fcell.2020.00336.
19. de Bhailís ÁM, Chrysochou C, Kalra PA. Inflammation and Oxidative Damage in Ischaemic Renal Disease. Antioxidants (Basel). 2021;10(6):845. DOI: 10.3390/antiox10060845.
20. Paragas N, Qiu A, Hollmen M, et al. NGAL-Siderocalin in kidney disease. Biochim

Biophys Acta. 2012;1823(9):1451-8. doi:10.1016/j.bbamcr.2012.06.014

21. Briguori C, Visconti G, Rivera NV, et al. Cystatin C and contrast-induced acute kidney injury. Circulation. 2010;121(19):2117–22. DOI: 10.1161/CIRCULATIONAHA.109.919639.

22. Andreucci M, Faga T, Riccio E, et al. The potential use of biomarkers in predicting contrast-induced acute kidney injury. Int J Nephrol Renovasc Dis. 2016;9:205-21. DOI: 10.2147/IJNRD.S105124.

23. Dalili N, Chashmniam S, Khoormizi SMH, et al. Urine and serum NMR-based metabolomics in pre-procedural prediction of contrast-induced nephropathy. Intern Emerg Med. 2020;15(1):95-103. DOI: 10.1007/s11739-019-02128-x.

24. Li S, Zheng Z, Tang X. Preprocedure and postprocedure predictive values of serum b2-microglobulin for contrast-induced nephropathy in patients undergoing coronary computed tomography angiography: a comparison with creatinine-based parameters and cystatin C. J Comput Assist Tomogr. 2015;39(6):969–74. DOI: 10.1097/RCT.0000000000000294.

25. Ahmed K, McVeigh T, Cerneviciute R, et al. Effectiveness of contrast-associated acute kidney injury prevention methods; a systematic review and network meta-analysis. BMC Nephrol. 2018;19(1):323. DOI: 10.1186/s12882-018-1113-0.

26. Yao YL, Gao Y. Present Situation and Research Progress of Kidney Function Recoverability Evaluation of Acute Kidney Injury Patient. Int J Gen Med. 2021;14:1919-1925. DOI: 10.2147/IJGM.S303348.

27. Andreucci M, Faga T, Riccio E, et al. The potential use of biomarkers in predicting contrast-induced acute kidney injury. Int J Nephrol Renovasc Dis. 2016;9:205-21. DOI: 10.2147/IJNRD.S105124.

28. Miao S, Xue ZK, Zhang YR, et al. Comparison of Different Hydration Strategies in Patients with Very Low-Risk Profiles of Contrast-Induced Nephropathy. Med Sci Monit. 2021;27:e929115. DOI: 10.12659/MSM.929115.

29. Cai L, Rubin J, Han W, et al. The origin of multiple molecular forms in urine of HNL/NGAL. Clin J Am Soc Nephrol. 2010;5(12):2229–35. DOI: 10.2215/CJN.00980110.

30. Charlton JR, Portilla D, Okusa MD. A basic science view of acute kidney injury biomarkers. Nephrol Dial Transplant 2014;29(7):1301–11. DOI: 10.1093/ndt/gft510.

31. Zhou F, Luo Q, Wang L, et al. Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: a meta-analysis. Eur J Cardiothorac Surg. 2016;49(3):746-55. DOI: 10.1093/ejcts/ezv199.

32. Haase-Fielitz A, Haase M, Devarajan P. Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: a critical evaluation of current status. Ann Clin Biochem. 2014;51(Pt 3):335-51. DOI: 10.1177/0004563214521795.

33. Ronco C. Biomarkers for acute kidney injury: is NGAL ready for clinical use? Crit Care. 2014;18(6):680. DOI: 10.1186/s13054-014-0680-0.

34. Clerico A, Galli C, Fortunato A, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as biomarker of acute kidney injury: a review of the laboratory characteristics and clinical evidences. Clin Chem Lab Med. 2012;50(9):1505–17. DOI: 10.1515/cclm-2011-0814.

35. Lupu L, Rozenfeld KL, Zahler D, et al. Detection of Renal Injury Following Primary Coronary Intervention among ST-Segment Elevation Myocardial Infarction Patients: Doubling the Incidence Using Neutrophil Gelatinase-Associated Lipocalin as a Renal Biomarker. J Clin Med. 2021;10(10):2120. DOI: 10.3390/jcm10102120.

36. da Veiga GL, da Costa Aguiar Alves B, Perez MM, et al. Kidney Diseases: The Age of Molecular Markers. Adv Exp Med Biol. 2021;1306:13-27. DOI: 10.1007/978-3-030-63908-2_2.

37. Quintavalle C, Anselmi CV, De Micco F, et al. Neutrophil gelatinase-associated lipocalin and contrast-induced acute kidney injury. Circ Cardiovasc Interv. 2015;8(9):e002673. DOI: 10.1161/CIRCINTERVENTIONS.115.002673.

38. Li Q, Huang Y, Shang W, et al. The Predictive Value of Urinary Kidney Injury Molecular 1 for the Diagnosis of Contrast-Induced Acute Kidney Injury after Cardiac Catheterization: A Meta-Analysis. J Interv Cardiol. 2020;2020:4982987. DOI: 10.1155/2020/4982987.

39. Sabbisetti VS, Ito K, Wang C, et al. Novel assays for detection of urinary KIM-1 in mouse models of kidney injury. Toxicol Sci. 2013;131(1):13-25. DOI: 10.1093/toxsci/kfs268.

40. Liao B, Nian W, Xi A, et al. Evaluation of a Diagnostic Test of Serum Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Urine KIM-1 in Contrast-Induced Nephropathy (CIN). Med Sci Monit. 2019;25:565-70. DOI: 10.12659/MSM.912569.

41. Li W, Yu Y, He H, et al. Urinary Kidney injury molecule-1 as an early indicator to predict contrast induced acute Kidney injury in patients with diabetes mellitus undergoing percutaneous coronary intervention. Biomed Rep. 2015;3(4):509–12. DOI: 10.3892/br.2015.449.

42. Wybraniec MT, Chudek J, Bozentowicz-Wikarek M, et al. Prediction of contrast-induced acute kidney injury by early post-procedural analysis of urinary biomarkers and intra-renal Doppler flow indices in patients undergoing coronary angiography. J Interv Cardiol. 2017;30(5):465–72. DOI: 10.1111/joic.12404.

43. Altmann C, Andres-Hernando A, McMahan RH, et al. Macrophages mediate lung inflammation in a mouse model of ischemic acute kidney injury. Am J Physiol Renal Physiol. 2012;302(4):F421-32. DOI: 10.1152/ajprenal.00559.2010.

44. Lin X, Yuan J, Zhao Y, et al. Urine interleukin-18 in prediction of acute kidney injury: a systemic review and meta-analysis. J Nephrol. 2015;28(1):7-16. DOI: 10.1007/s40620-014-0113-9.

45. Banda J, Duarte R, Dix-Peek T, et al. Biomarkers for Diagnosis and Prediction of Outcomes in Contrast-Induced Nephropathy. Int J Nephrol. 2020;2020:8568139. DOI: 10.1155/2020/8568139.

46. He H, Li W, Qian W, et al. Urinary interleukin-18 as an early indicator to predict contrast-induced nephropathy in patients undergoing percutaneous coronary intervention. Exp Ther Med. 2014;8(4):1263–6. DOI: 10.3892/etm.2014.1898.

47. Rear R, Bell RM, Hausenloy DJ. Contrast-induced nephropathy following angiography and cardiac interventions. Heart. 2016 Apr;102(8):638-48. DOI: 10.1136/heartjnl-2014-306962.

48. Lichosik M, Jung A, Jobs K. Interleukin 18 and neutrophil-gelatinase associated lipocalin in assessment of the risk of contrast-induced nephropathy in children. Cent Eur J Immunol. 2015;40(4):447–53. DOI: 10.5114/ceji.2015.56967.

49. Roberts LM, Buford TW. Lipopolysaccharide binding protein is associated with CVD risk in older adults. Aging Clin Exp Res. 2021;33(6):1651-8. DOI: 10.1007/s40520-020-01684-z.

50. Fujita D, Takahashi M, Doi K, et al. Response of urinary liver-type fatty acid-binding protein to contrast media administration has a potential to predict oneyear renal outcome in patients with ischemic heart disease. Heart Vessels 2015;30(3):296–303. DOI: 10.1007/s00380-014-0484-9.

51. Hishikari K, Hikita H, Nakamura S, et al. Urinary Liver-Type Fatty Acid-Binding Protein Level as a Predictive Biomarker of Acute Kidney Injury in Patients with Acute Decompensated Heart Failure. Cardiorenal Med. 2017;7(4):267-75. DOI: 10.1159/000476002.

52. Menez S, Parikh CR. Assessing the health of the nephron in acute kidney injury: biomarkers of kidney function and injury. Curr Opin Nephrol Hypertens. 2019;28(6):560-6. DOI: 10.1097/MNH.0000000000000538.

53. Kamijo-Ikemori A, Hashimoto N, Sugaya T. Elevation of urinary liver-type fatty acid binding protein after cardiac catheterization related to cardiovascular events. Int J Nephrol Renovasc Dis 2015; 8: 91–99. DOI: 10.2147/IJNRD.S88467.

54. Qin C, Li M, Bai T, et al. Tisp40 deficiency limits renal inflammation and promotes tubular cell proliferation in renal ischemia reperfusion injury. Exp Cell Res 2018;371(1):255-261. DOI: 10.1016/j.yexcr.2018.08.019.

55. Sato W, Sato Y. Midkine in nephrogenesis, hypertension and kidney diseases. Br J Pharmacol 2014;171(4):879-887. DOI: 10.1111/bph.12418.

56. Malyszko J, Bachorzewska-Gajewska H, KocZorawska E. Midkine: a novel and early biomarker of contrast-induced acute kidney injury in patients undergoing percutaneous coronary interventions. Biomed Res Int 2015;2015:879509. DOI: 10.1155/2015/879509.

57. Schunk SJ, Zarbock A, Meersch M, et al. Association between urinary dickkopf-3, acute kidney injury,and subsequent loss of kidneyfunction in patients undergoing cardiac surgery: an observational cohort study. Lancet 2019;394(10197):488–496. DOI: 10.1016/S0140-6736(19)30769-X.

58. Zou YF, Zhang W. Role of microRNA in the detection, progression, and intervention of acute kidney injury. Exp Biol Med (Maywood). 2018;243(2):129-136. DOI: 10.1177/1535370217749472.

Author information:

Lavrischeva Yulia V., PhD, Senior Researcher, Research Laboratory of Pathogenesis and Therapy of Arterial Hypertension, Almazov National Medical Research Centre;

Konradi Alexandra O., MD, Dr. Sc., Professor, Corresponding Member RAS, Deputy General Director for Research, Head of the Research Department of Arterial Hypertension, Head of the Department of Management Organization and Health Economics, Institute of Medical Education, Almazov National Medical Research Centre;

Yakovenko Alexander A., PhD, Associate Professor of the Department of Nephrology and Dialysis of the Faculty of Postgraduate Education, Academician I. P. Pavlov First Saint Petersburg State Medical University.