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CONTRAST-INDUCED ACUTE KIDNEY INJURY: MECHANISM AND MARKERS OF RENAL TISSUE DAMAGE (LITERATURE REVIEW)

Actuality. *Transcatheter contrast interventional and diagnostic procedures are becoming increasingly common in use, given their microinvasiveness, breadth of diagnostic capabilities, rapid recovery, and significant improvement in patients' quality of life at a relatively low cost. However, the use of contrast is associated with the occurrence of secondary acute kidney injury, which in turn can lead to a decrease in the number of favorable prognoses and sometimes to fatalities. In their routine practice, doctors try to take a careful approach to the choice of contrast examination methods, based on the presence of comorbid pathology and renal functional capacity, however, in urgent cases, there is not always time and means for a complete analysis of the clinical situation. Most procedures require intravascular administration of contrast media, which is associated with an increased incidence of contrast-induced/contrast-associated acute kidney injury. Ongoing research continues to shed light on the pathological mechanisms by which contrast agents affect renal tissue and numerous studies are now identifying the new biomarkers that may facilitate earlier diagnosis. These developments are of particular interest to physicians across various specialties. A deeper understanding of these mechanisms may lead to the development of more effective preventive strategies, while the integration of biomarker testing into clinical workflows could enable prompt detection and management of emerging renal pathologies.*

The aim of the research is *to analyze the recent literature and relevant online sources, to determine the underlying mechanisms and biomarkers of kidney injury associated with contrast agents used in interventional and diagnostic procedures.*

Material and methods. *This review is based on an analysis of recent peer interviewed publications focused on elucidating the pathophysiological mechanisms, underlying contrast-induced kidney injury and identifying new biomarkers indicative of renal damage caused by contrast media.*

Results and their discussion. *Contrast-induced acute kidney injury remains a complex multifaceted condition involving diverse pathological mechanisms. Expanding knowledge about the renal effects of contrast agents provides opportunities for the development of new therapeutic and preventive strategies. The creatinine level, currently used as the primary marker of kidney injury, unfortunately does*

not offer a comprehensive understanding of the extent and severity of renal damage. It is also influenced by numerous confounding factors, including age, sex, body weight and muscle mass. The incorporation of new biomarkers of kidney injury holds promise for delivering more detailed information regarding glomerular filtration status, the presence of inflammation, tubular function and compensatory renal capacity. These advancements enable improved risk stratification for timely intervention and enhanced clinical prognosis.

Conclusion. *Contrast-induced acute kidney injury is a known complication of intravascular contrast media administration. The underlying mechanisms are strongly associated with the physiochemical properties and concentration of the contrast agents used. Despite many studies, the full spectrum of renal alterations caused by contrast exposure has yet to be completely elucidated. The prognosis and prevention of contrast-induced acute kidney injury are directly linked to ongoing research and the clinical implementation of new biomarkers for early detection of renal tissue damage. Continued investigation into risk factors, pathophysiological mechanisms and the development of effective diagnostic, preventive and therapeutic strategies should be a primary focus in modern medical practice. The doctors' action algorithm should include risk assessment, use of validated biomarkers, preventive measures, and monitoring of the patient's condition.*

Key words: *contrast-induced acute kidney injury, nephropathy, pathogenesis, markers.*

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КОНТРАСТ-ІНДУКОВАНЕ ГОСТРЕ ПОШКОДЖЕННЯ НИРОК: МЕХАНІЗМ ТА МАРКЕРИ УРАЖЕННЯ НИРКОВОЇ ТКАНИНИ (ОГЛЯД ЛІТЕРАТУРИ)

Актуальність. *Транскатетерні контрастні інтервенційні та діагностичні процедури набувають усе більшої поширеності у використанні, зважаючи на свою мікроінвазивність, широту діагностичних можливостей, швидкість відновлення працездатності та значне покращення якості життя пацієнтів на тлі відносно невеликої вартості. Незважаючи на це, використання контрасту пов'язане з виникненням вторинного, гострого пошкодження нирок, що, своєю чергою, здатне спричиняти зменшення кількості сприятливих прогнозів, а іноді призводити до летальних випадків. У своїй рутинній практиці лікарі намагаються виважено підходити до вибору контрастних методів обстежень, спираючись на наявність коморбідної патології та функціональну здатність нирок, проте в ургентних випадках не завжди є час та засоби для повного*

аналізу клінічної ситуації. Більшість процедур вимагає внутрішньосудинного введення контрастної речовини, що пов'язано зі збільшенням виникнення випадків гострого ураження нирок, спричиненого контрастом. Результати дослідження механізму патогенетичного впливу контрасту на ниркову тканину постійно оновлюються, також з'являються дані про нові маркери такого впливу, що є предметом зацікавленості лікарів різних спеціальностей. Розуміння механізмів дасть можливість розробити дієві методи профілактики цього ускладнення, а впровадження маркерних проб –вчасно виявити патологію, що розвивається.

***Мета дослідження** – на підставі аналізу літературних даних останніх років та доступних інтернет-ресурсів визначити механізми та маркери ураження нирок як наслідок дії контрастних речовин після інтервенційних втручань та діагностичних процедур.*

***Матеріали та методи.** Авторами проведений аналіз новітніх літературних джерел з проблем висвітлення патогенетичних механізмів патологічного впливу контрастних речовин на ниркову тканину та виявлення нових маркерів ушкодження нирок під їх впливом.*

***Результати дослідження та їх обговорення.** Контраст-індуковане гостре пошкодження нирок залишається складною багаторівневою проблемою з різними патологічними механізмами. Поглиблення знань про вплив контрасту дає можливості дослідження нових методів терапії та профілактики цього ускладнення. Рівень креатиніну, який дотепер використовується як маркер ушкодження, на жаль, не дає вичерпного розуміння про рівень та глибину ураження, а також залежить від багатьох супутніх факторів, таких як вік, стать, маса тіла та ін. Імплементація нових знань про маркери пошкодження нирок здатна надати величезну кількість додаткової інформації про стан клубочкової фільтрації, наявність запального компонента, функціонування тубулярного апарату, компенсаторні здібності організму. Також з'являється можливість стратифікації ризику хронізації процесу та розвитку летальних випадків, що дозволить вчасно провести профілактику та покращити прогноз.*

***Висновки.** Контраст-індуковане гостре пошкодження нирок є ускладненням внутрішньосудинного введення контрастних речовин. Механізм впливу контрасту безпосередньо пов'язаний з фізико-хімічними особливостями та концентрацією розчину. Проведені численні дослідження досі не дають повної відповіді на весь спектр змін, які відбуваються під впливом контрастних речовин. Прогноз та профілактика ускладнень використання контрасту безпосередньо залежать від дослідження та імплементації в практичну діяльність лікарів нових маркерів ушкодження ниркової тканини. Дослідження факторів ризику, патогенезу та розробка ефективних діагностичних, профілактичних і лікувальних заходів повинні стати провідними в умовах сучасної медичної практики. Алгоритм дій лікарів повинен включати оцінку ризику використання валідованих біомаркерів, профілактичні заходи та моніторинг стану пацієнта.*

***Ключові слова:** контраст-індуковане гостре пошкодження нирок, нефропатія, патогенез, маркери.*

Relevance. Contrast-induced nephropathy (CIN) or contrast-induced acute kidney injury (CI-AKI) is an iatrogenic acute injury to renal tissue, the development of which is observed after intravascular, mostly intraarterial, administration of contrast agents (CAs) for diagnostic procedures or therapeutic angiographic interventions (Kusirisin et al., 2020). This pathology is defined as impaired renal function, manifested by either an increase in serum creatinine (SCr) of 25% from baseline or an increase in absolute SCr of 0.5 mg/dL (44 μmol/L) within 48–72 hours after intravenous contrast administration (Moro et al., 2021; Davenport et al., 2020).

CIN is becoming a significant problem due to the increase in the number of coronary angiographies and interventional procedures using contrast agents in high-risk patients with chronic kidney disease, diabetes mellitus, hypertension, and renal failure, due to the development of contrast-induced damage to renal structures. Rapid deterioration of renal function may result from coronary angiography or percutaneous coronary intervention (Modi et al., 2025).

To describe the nature of the relationship between contrast administration and the development of AKI, the American College of Radiology has proposed the following terms: post-contrast kidney injury, contrast-induced, and contrast-associated acute kidney injury (Davenport et al., 2020). The term "post-contrast renal injury" describes a decrease in renal function within 48 hours after intravascular administration of a contrast agent. Contrast-associated acute kidney injury is any AKI that occurs within 48 hours of contrast medium administration. These terms are synonymous and represent a correlative diagnosis. None of them suggests a causal relationship between contrast administration and the development of AKI. The term "contrast-induced acute kidney injury" refers to the development of pathology resulting from the administration of contrast media. If it is clear that there is a causal relationship between the administration of contrast media and the appearance of signs of AKI, it is recommended to use the term "contrast-induced acute kidney injury" (Li, Wang, 2024; Jones et al., 2025). In healthy people, the incidence of CIN is less than 1%, but in people with pre-existing renal failure or additional risk factors such as diabetes, hypertension, advanced age, and cardiovascular disease, the incidence of this complication can reach 15% (Wang, et al., 2024). Since patients with existing comorbid conditions always have the potential to develop contrast-related renal tissue damage, physicians are usually quite cautious in choosing these examination methods (Bobyryov et al., 2017). At the same time, in the development of urgent, life-threatening emergencies, the use of contrast diagnostic methods is of great importance and is performed according to vital indications, outlining the scope of endovascular intervention. Although CIN often manifests as transient acute kidney injury, in

some cases chronic renal decompensation or even death can develop.

The aim of the study is to analyze the recent literature and relevant online sources, to determine the underlying mechanisms and biomarkers of kidney injury associated with contrast agents used in interventional and diagnostic procedures.

Materials and methods. This review is based on an analysis of recent peer interviewed publications focused on elucidating the pathophysiological mechanisms, underlying contrast-induced kidney injury and identifying new biomarkers indicative of renal damage caused by contrast media.

Results and discussion. Currently, there are four types of contrast agents. High-osmolar ionic monomers, low-osmolar: ionic dimers and non-ionic monomers, as well as isoosmolar non-ionic dimers. Ionic CAs have a tri-iodinated benzene ring with a carboxyl group in the form of a salt with sodium or methylglucamine, they have an osmolarity approximately five times higher than the osmolarity of human blood plasma, causing excessive hemodilution, endothelial damage, and have a pronounced nephrotoxic effect. Nonionics CAs do not dissociate in solution and contain three iodine atoms per molecule, which implies a lower osmolarity. Nonionic CAs with low osmolarity are better tolerated and are associated with a lower risk of adverse reactions (Najjar, 2024).

Among nonionic CAs, iodixanol is a dimer with six iodine atoms and has an osmolarity similar to that of plasma with a lower incidence of adverse effects than monomer molecules (Jenerowicz et al., 2022; McDonald & McDonald., 2023). The only ionic CAs with low osmolarity is the dimer ioxaglate, which has an osmolality similar to nonionic monomers but does not provide a low incidence of adverse reactions due to the chemotoxic effect of electrical charges (Brillantino et al., 2020).

The pharmacokinetic properties of a contrast agent are determined by several factors: the side chains of the aromatic rings affect solubility, osmolarity, protein binding, and toxicity profile. Lipophilic side chains reduce water solubility and provide a level of binding to plasma proteins, while the carboxyl group can form salts and increase both solubility and osmolarity. Hydrophilic side chains, such as acetamide groups and polyhydroxylated groups, further improve water solubility, tolerability, and the ability to reduce binding to blood plasma proteins. The last property is important for ensuring rapid glomerular filtration. Nonionic CAs are typically very hydrophilic and are characterized not only by low osmolarity, the absence of electrical charges, but also by the presence of a larger number of hydrophilic side chains that increase the solubility of molecules.

A more uniform distribution of hydroxyl groups in nonionic contrast agents limits the interaction of lipophilic regions of the molecule with plasma proteins and cell membranes and improves contrast tolerability (Brillantino et al., 2020; Hawthorne et al., 2022).

The next main characteristic of a contrast agent solution is the iodine concentration, i.e. the number of iodine atoms contained in a unit volume, expressed in mgI/ml. The higher the iodine concentration in the contrast, the greater the enhancement. Computed tomography (CT) uses non-ionic contrast agents with iodine concentrations of 300 to 400 mgI/ml.

Finally, an important property of contrast media is viscosity, i.e. its ability to fill vessels, needles and injection catheters. High viscosity prevents the rapid administration of large volumes of contrast, especially in angio-CT studies, and also prolongs the transit time of the contrast media in the microcirculation and in the renal tubules with subsequent damage to the endothelium and kidneys (Brillantino et al., 2020). The viscosity of the solution increases with increasing molecular size and iodine concentration and decreases with increasing temperature.

Specific properties of CAs solutions, such as high osmolarity, can increase the intrinsic cytotoxicity of the solution: the higher the osmolarity of the media, the higher the toxicity of iodine at a given concentration (Metrard, et al., 2024). Elevated blood glucose concentration also enhances the oxidative response induced by CAs in renal mesangial cells (Wang et al., 2024).

Despite numerous studies, the pathophysiological mechanisms of CIN development are not fully understood. The pathogenesis is multicomponent and includes a variety of molecular and biochemical changes. It should be noted that the presence of risk factors such as diabetes mellitus, coronary heart disease, existing kidney disease and hypertension, and old age contribute to the severity and frequency of renal complications. Currently, several explanations for the mechanisms of kidney damage have been proposed, including direct damaging effects, indirect damaging effects, and production of reactive oxygen species (ROS).

Endothelial cells play a key role in maintaining vascular homeostasis. Their function includes controlling vascular tone, inflammation activity, and thrombogenesis (Wang, He, 2024). Vasculopathy with impaired vascular endothelial function is a typical feature of CIN (Kumar et al., 2023). Under the influence of CAs, the production of vasodilators such nitric oxide (NO) and prostaglandin I2 (PGI2) is suppressed, against the background of increased formation of endothelin-1 in endothelial cells, which leads to vasoconstriction and ischemia of renal

tissue. Endothelial dysfunction reduces the anti-inflammatory and antithrombotic properties of vessels and contributes to the development of systemic organ-specific complications due to the administration of CAs (Pustovoyt et al., 2025; Wang, He, 2024; Sarychev et al., 2022; Skrypnyk et al., 2017). As a result of CAs using, there is an increase in the production of reactive oxygen species (ROS) and the expression of adhesion molecules with the secretion of inflammatory factors (Kusirisin, et al., 2020), renal tubular epithelial cells also undergo damage and apoptosis, causing significant tubular dysfunction (Li, Wang, 2024; Chmielewski et al., 2024).

Almost all CRs have a direct cytotoxic effect on vascular endothelial cells and renal tubular epithelial cells, which ultimately manifests itself in a violation of cellular integrity (Theofilis, Kalaitzidis, 2024; Moisieieva et al., 2024). Damage to the vascular endothelium reduces blood flow velocity in the renal capillaries and leads to renal medullary hypoxia and tubular insufficiency (Li, Wang, 2024).

The shedding of necrotic epithelial cells into the tubular lumen disrupts the integrity of the barrier between the peritubular interstitium and the filtrate, increases intraluminal pressure and permeability, and causes backflow into the interstitium. In response to epithelial destruction, an immune response is initiated, provoking the secretion of inflammatory mediators and vasopressors. The main source of inflammation-associated molecules and pro-inflammatory factors is epithelial barrier dysfunction, thus this process contributes to the development of refractory inflammation with worsening renal tubular dysfunction (Kellum et al., 2021).

A group of immunostimulatory molecules that participate in the inflammatory response after tissue damage is defined as damage-associated molecular patterns (DAMPs). Uromodulin, or Tamm-Horsfall glycoprotein, is a kidney-specific DAPMs. Its release is observed when the integrity of the tubular apparatus is disrupted, and it is expressed exclusively by epithelial cells of the ascending limb of the loop of Henle and the distal convoluted tubule (Karagiannidis et al., 2024). Physiological functions of this molecule are extremely varied. Among them are the regulation of the renal outer medullary potassium channel, calcium and magnesium homeostasis, and blood pressure control (LaFavers et al., 2022; Kipp, Olinger, 2020), formation of casts in urine, protection against kidney stone formation by reducing calcium crystal aggregation, inhibition of urinary tract infections (Thielemans et al., 2023) and many others. The immunomodulatory function of uromodulin consists in direct activation of TLR4 and promotion of maturation of competent cells (Nourie et al., 2024). Both in the kidneys and in the body as a whole, under its influence, the production of ROS is suppressed (Nanamatsu et al., 2024), and in the kidney interstitium, pro-inflammatory signaling is inhibited.

Serum uromodulin concentrations are inversely correlated with C-reactive protein (CRP) and IL-1β levels, regardless of renal function (Li et al., 2024). Its high serum concentration is associated with a favorable metabolic profile, a reduced likelihood of developing acute kidney injury (You et al., 2021). Acting as a marker of tubular secretion, uromodulin reflects, residual nephrons mass. A decrease in the mass of tubular cells leads to a reduce in the release of this glycoprotein. In conditions of uromodulin deficiency, activation of urate transporters occurs, which is manifested by hyperuricemia (Micanovic et al., 2020). A decrease in uromodulin level indicates kidney damage or loss of function and is associated with adverse outcomes (Melchinger et al., 2022).

Tubular necrosis is manifested by acute kidney injury, which releases nonspecific DAMPs (histones and amphoterin), increases vascular permeability, which potentiates and deepens shock and hypoperfusion through Toll-like receptors activation. Cellular damage increases oxidative stress and free radical formation. This process consumes nitric oxide, neutralizing its protective effect as a vasodilator (Kozlov et al., 2024).

Under conditions of prolonged vasoconstriction, glomerular filtration rate (GFR) decreases, medullary hypoperfusion develops, and blood viscosity increases in the nephron vessels (Theofilis, Kalaitzidis, 2024).

One of the main mechanisms of hypoxia in the medullary area is a decrease in regional microcirculation against the background of an increase in the oxygen demand of tubular cells. The deep part of the renal medulla, containing the metabolically active thick ascending parts of Henle's loop, is the most vulnerable to hypoxic damage. Here, an osmotic gradient is created by active sodium reabsorption, which requires a large amount of oxygen. Due to the osmotic load and the effect of endothelin release under the influence of CAs, sodium reabsorption by distal tubular cells increases, which leads to increased oxygen consumption. Contrast administration transiently increases renal plasma flow, glomerular filtration, and urine output, followed by a sustained decrease to about a quarter below baseline. The higher the osmolality of the substance, the stronger these effects are manifested (Somkereki et al., 2024).

Contrast agents shift the balance between vasodilator and vasoconstrictor factors toward vasoconstriction and lead to medullary hypoperfusion primarily through constriction of the descending medullary vessels, which are lined with pericytes (Durante et al., 2024). The bioavail-

ability of nitric oxide in the descending vasa vasorum, whose average size is close to the diameter of erythrocytes, decreases, and the concentration of superoxide increases (Theofilis, Kalaitzidis, 2024). Iodixanol has a more pronounced vasoconstrictive effect on afferent than on efferent arterioles. Decreased NO availability and increased superoxide concentration explain the increased tone and reactivity of afferent arterioles (Fountain et al., 2025). Medullary hypoperfusion interferes with oxygen transport, causing ischemic tubular damage and maintaining a vicious cycle. All types of CAs cause similar degrees of renal medullary vasoconstriction (Modi et al., 2025).

Water-soluble CAs can damage the kidneys due to differences in osmolarity relative to surrounding tissues. The higher the osmolarity of the solution, the greater its cytotoxic effect. It should be noted that the osmolarity of the renal medulla is higher than in other tissues. Contrast agents are significantly diluted in the lumen of the vessel before they reach the kidneys, which reduces their osmolality. In the kidneys, they are freely filtered in the glomeruli, but cannot be reabsorbed by the tubules. As water is reabsorbed along the length of the tubule, the CAs becomes increasingly concentrated, increasing its osmolarity and viscosity in the tubule. The high viscosity of the tubular fluid causes an increase in resistance, which increases tubular pressure and interferes with glomerular filtration. The increase in resistance markedly slows tubular flow, (Shams, Mayrovitz, 2021) and the intrarenal residence time of CAs becomes much longer. Highly viscous CAs have a longer contact time with tubular epithelial cells, which deepens tubular damage (Kusirisin et al., 2023). Increased pressure in the tubules stretches them and increases renal interstitial pressure due to the strong renal capsule. As a result, the renal vessels, including the narrow descending vessels, are compressed. This increase in vascular resistance further exacerbates medullary hypoperfusion. The decrease in urine flow rate increases the duration of action of the contrast agent, thus enhancing its cytotoxic effect (Ehmann et al., 2023).

Intrarenal vasoconstriction, mediated by increases in vasoconstrictor mediators, including renin, angiotensin II, and endothelin, together with decreases in vasodilatory mediators, including nitric oxide and PGI2, exacerbates medullary hypoxia (Leisman, 2020).

Oxidative stress plays a significant role in the progression of CIN. Hypoxia can lead to decreased oxidative phosphorylation and increased production of free radicals in mitochondria (Zhang et al., 2020).

Impaired kidney function under the influence of CR also occurs due to excessive production of ROS against the background of a decrease in the activity of antioxidant mechanisms. Once the ability of cells to absorb ROS is exceeded, they lead to so-called ischemia-reperfusion injury: cell damage caused by the combined effects of hypoxia and ROS-mediated oxidative damage. The latter affects mitochondrial and nuclear DNA, membrane lipids, and cellular proteins. Oxidative stress of the endoplasmic reticulum of kidney cells can lead to plasma membrane damage and mitochondrial dysfunction (Ricciardi, Gnudi, 2020), which potentiates ROS production by catalytically releasing iron with subsequent activation of the Haber-Weiss and Fenton reactions (Cheng, Li, 2023), damaged mitochondria release cytochrome C, which is closely linked to the activation of apoptosis (Luo et al., 2023). During oxidative stress of the endoplasmic reticulum, cytosolic Ca2+ overload develops due to the generation of ROS, which causes irreversible cell death. Under conditions of medullary hypoxia, ROS are also increased, which stimulates mitochondrial oxidative stress and mitochondrial dysfunction (Mahapatro et al., 2024).

In general, ROS play an important role in altered renal microcirculation. They induce and enhance vasoconstriction caused by angiotensin-II and endothelin-I, an important vasoconstrictor associated with oxidative damage to endothelial cells. Its high level increases the risk of CIN. In addition, they reduce the bioavailability of vasodilator NO (Davenport et al., 2020).

Nicotinamide adenine dinucleotide phosphate oxidase (NOX), which is a source of reactive oxygen species, can serve as a marker of epithelial and endothelial cell damage (Hong et al., 2024). The highest ratio of hydrogen peroxide to superoxide is provided by NOX4, the upregulation of whose protein expression is associated with increased oxidative stress. Iodixanol enhances the expression of NOX4 and increases the generation of ROS in renal tubular cells, causing their apoptosis and necrosis (Guo et al., 2021). Endothelial nitric oxide synthase (eNOS) is a homodimer that binds many different cofactors, converting L-arginine and oxygen into L-citrulline and nitric oxide (Momot et al., 2024). Dysregulation and uncoupling of eNOS may be facilitated by aberrant activation of NOX, leading to reduced nitric oxide bioavailability, formation of superoxide and endogenous peroxynitrite, creating a toxic cycle of oxidative stress and, exacerbated endothelial dysfunction (Deng et al., 2024). Under the influence of iodixanol, abnormal phosphorylation of eNOS occurs, further reducing nitric oxide production and increases the formation of peroxynitrite in endothelial cells (Buria et al., 2024; Guo et al., 2021; Yelins'ka et al., 2019).

Ferroptosis, or iron-dependent programmed cell death, is gaining an increasingly recognized role in the development of CIN due to the accumulation of ROS

in lipids with their subsequent fatal peroxidation. Classical ferroptosis inhibitors effectively increase cell viability and significantly reduce ROS production in CIN, and also inhibit the development of renal dysfunction, prevent ROS production, and reduce iron accumulation. These data may in the future help to better understand the molecular mechanisms of CIN and develop new therapeutic and preventive strategies (Zhu et al., 2024).

Cellular damage provokes an inflammatory response, which later leads to changes in homeostasis in the renal systems and in the circulation. The immune response caused by CAs toxicity can significantly increase the migration of immune cells and the accumulation of cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) (Cobley, Husi, 2020). An early sign of CIN is an inflammatory response induced by various cell types. Upregulation of cytokines such as TNF-α, interleukin-1 (IL-1), interleukin-18 (IL-18), tumor growth factor-beta (TGF-β), interferon gamma (IFN-γ), interleukin-6 (IL-6), and interleukin-33 (IL-33) positively correlates with increased proteinuria, especially in diabetes mellitus (Li, Ren, 2020). Endothelial cell dysfunction caused by cytotoxic CAs activates relevant signaling pathways and leads to the development of systemic inflammation (Hojjat, Wiwit, 2024).

The role of cytokines in the development of CIN is well established. For example, IL-6, which is involved in the regulation of an extremely large number of biological processes such as the acute phase response of inflammation and the immune response, is mainly produced in podocytes. Depending on the dose and time, its concentration increases under the influence of pro-inflammatory mediators (Shankland et al., 2023). Podocytes are one of the few kidney cells that can express the IL-6 receptor. At the same time, IL-6 induces autocrine podocyte proliferation (Shahzad et al., 2022). IL-6 secretion and signal transduction in podocytes is increased and initiated by high glucose levels (Reddy et al., 2024).

Mesangial cells are also capable of secreting IL-6. Among other things, due to this, they are activators of cellular inflammation, participate in the regulation of the immune response and in metabolically mediated kidney damage (Fu et al., 2024).

Common stimulators of endothelial cells to generate IL-6 are inflammatory mediators such as IL-1, TNFα, and IL-4. The interaction between IL-6 and endothelial cells is mediated by trans-signaling and involves leukocyte recruitment and chemokine secretion. The generation process promotes the expression of the angiotensin II receptor type 1 gene, which is accompanied by vasoconstriction and ROS production, and, as a result, endothelial dysfunction (Tona et al., 2024).

Damage to the renal glomeruli is an inducer of IL-6 production in tubulointerstitial cells (Hao et al., 2024). There is a close relationship between its expression and AKI. IL-6 signaling is enhanced after bilateral renal tissue ischemia, linking local and systemic inflammation and can be used as a biomarker for AKI (Katkenov et al., 2024).

In toxic AKI, IL-6 expression is significantly increased mainly in renal tubulointerstitial cells and strongly correlates with renal injury. In contrast, IL-6 deficiency attenuates neutrophil recruitment to the lesion site and causes relative renal tissue resistance. One of the central mechanisms of AKI is IL-6-mediated activation of neutrophils, which can be induced after activation by triggering the netosis system with damage including to the endothelium within the renal microcirculation (Wu et al.; 2022, Wang et al., 2023). Stimulation of IL-6 trans-signaling reduces the extent of renal tissue damage and preserves function by reducing the activity of the main oxidative stress mechanism (Yan et al., 2023; Lutsenko et al., 2017).

Toll-like receptors (TLRs) play a leading role in the implementation of immune responses. In diabetes, oxidative stress promotes the expression of TLR2 and TLR4 in monocytes, increasing the expression of cytokines, including IL-1 beta, IL-6, etc. (Li, Ren, 2020). This process is of great importance in enhancing the pro-inflammatory response in diabetes, which may contribute to the development of CIN (Shayan, Elyasi, 2020).

TLR4 plays an indispensable role in the pathogenesis of acute kidney injury and is the receptor primarily responsible for the inflammatory response (Jha et al., 2021; Yang et al., 2020). TLR4 expression occurs in mesangial cells, podocytes, endothelial cells, and tubular epithelial cells, where the transcriptional regulation of numerous pro-inflammatory cytokines and chemokines is localized, leading to renal inflammation (Cheng, Li, 2023). Increased renal damage may occur through the generation of inflammatory cytokines due to contrast-induced activation of Toll-like receptor 4 (TLR4), resulting in the induction of the downstream nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 3 (Nlrp3) inflammasome and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway (Holze et al., 2024).

Ca-binding proteins have shown potential ability to activate the TLR4 signaling axis (Weifeng et al., 2024). The Ca-binding protein S100A8/A9 is the most abundant structure associated with molecular damage. It is an endogenous ligand for TLR4 in the development of CIN. TLR4 binds to these proteins and activates the TLR4/

Nlrp3 pathway to induce the inflammatory cascade of kidney damage (Cheng, Li, 2023).

There is currently no specific biomarker that can accurately diagnose ACI in the early stages. Serum creatinine is widely used, but has significant limitations, as it depends, among other things, on gender, age, and muscle mass. Its serum level may not increase until the kidneys have suffered significant, and sometimes critical, damage. New studies are currently being conducted to find modern markers of kidney tissue damage that would help to timely detect and predict complications during contrast administration. In the PRESERVE cohort study, the following biomarkers were measured in plasma and urine of patients with chronic kidney disease one to two hours before angiography: monocyte chemotactic protein-1 (MCP-1), kidney injury molecule 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), IL-18, uromodulin (UMOD), and chitinase-3-like protein 1 (YKL-40). Patients with high plasma levels of KIM-1, lipocalin, and YKL-40 before contrast administration were found to be at increased risk of developing significant renal adverse events and death within 90 days. The markers IL-18, MCP-1, and YKL-40 were also correlated with higher mortality. Plasma KIM-1 was significantly higher in patients with contrast-induced AKI (Parikh et al., 2020).

KIM-1 is a glycoprotein that is activated in the proximal renal tubules following injury. The presence of a soluble, released form of KIM-1 in urine is associated with acute tubular necrosis, giving it the status of a marker of proximal tubular injury (Nourie et al., 2024).

The concentration of YKL-40 in blood plasma is linearly correlated with the severity of ACI and the level of pro-inflammatory markers, its borderline concentrations are a predictor of adverse outcomes and high mortality (Albeltagy et al., 2020). YKL-40 is probably closely related to immune-mediated, infectious, or mechanically induced endothelial dysfunction, which provides valuable information about the state of the renal vasculature and its changes in various pathologies (Amatruda et al., 2022; Knyazkova et al., 2023; Gutiérrez et al., 2022; Blazevic et al., 2024).

Considering the protective function of uromodulin, a decrease in its level in urine is associated with more pronounced lesions, such as interstitial fibrosis, tubular atrophy and glomerulosclerosis, and is negatively correlated with the level of inflammatory biomarkers: IL-6, TNFα and lipocalin 2 (Melchinger et al., 2022), which is the earliest biomarker detected in urine in kidney damage. Detection of urinary lipocalin 2 of plasma origin is possible only in case of the proximal renal tubules damage, or when its synthesis exceeds the tubular reabsorption capacity, as it is completely reabsorbed by the proximal tubules after free filtration (Puthumana et al. 2024).

One of the pro-inflammatory cytokines considered as a possible marker of acute kidney injury is IL-18, which is synthesized by renal macrophages. Its presence has been detected in various parts of the tubular system of the nephron. IL-18 levels are significantly elevated in the urine of patients with acute tubular necrosis compared with patients with urinary tract infections, prerenal acute renal failure, chronic kidney disease, and nephrotic syndrome (Luan et al., 2022).

Cystatin C, produced by all nucleated cells, is a well-known indicator of renal filtration and reabsorption function. Its plasma levels are independent of age, sex, muscle mass, and dietary habits, which is a significant difference from creatinine levels. Cystatin C is freely filtered in the kidneys without being secreted or taken up by cells. Almost all of it is normally reabsorbed and metabolized in the proximal tubule, resulting in its absence in the urine under normal conditions (Pottel et al., 2023).

The prognostic value of tissue inhibitor of metalloprotease-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) cannot be overestimated. They are constantly expressed in tubular cells and are detected in the urine as early as 4 hours after kidney injury (Esmeijer et al., 2021).

In recent years, increasing attention has been paid to the study of extracellular signaling molecules and mRNAs in the development of CIN. They may become promising therapeutic targets for the treatment and prevention of this complication in the future (Piedrafita et al., 2022; Grange, Bussolati, 2022; Aktas et al., 2025).

Thus, in summary, the most clinically ready markers of kidney damage are NGAL, KIM-1, Cystatin C, and TIMP-2/IGFBP7, while YKL-40, IL-18, MCP-1, and UMOD remain promising but require additional validation.

Conclusions. Contrast-induced acute kidney injury is a known complication of intravascular contrast media administration. The underlying mechanisms are strongly associated with the physiochemical properties and concentration of the contrast agents used. Despite many studies, the full spectrum of renal alterations caused by contrast exposure has yet to be completely elucidated. The prognosis and prevention of contrast-induced acute kidney injury are directly linked to ongoing research and the clinical implementation of new biomarkers for early detection of renal tissue damage. Continued investigation into risk factors, pathophysiological mechanisms and the development of effective diagnostic, preventive and therapeutic strategies should be a primary focus in modern medical practice.

To prevent and timely detect contrast-induced kidney injury in clinical practice, it is necessary to follow a certain algorithm of actions, which includes assessing the presence of risk factors (chronic kidney disease, diabetes, cardiovascular pathologies, advanced age, hypertension), assessing basic indicators of kidney function (creatinine, Cystatin C, glomerular filtration rate), type and dose of contrast agent, its osmolarity and viscosity at the stage before using the contrast. For timely detection of damage, it is recommended to use NGAL, KIM-1 and Cystatin C as primary markers. In high-risk patients, it is advisable to use TIMP-2/IGFBP7 to predict the development of AKI. Additional markers (IL-18, MCP-1, YKL-40, UMOD) can be used in research or specialized centers to clarify the pathogenesis. It is necessary to ensure adequate hydration before and after the procedure, use the minimum effective dose of contrast, and prefer less nephrotoxic agents (non-ionic low-osmolar). Repeated contrast studies within a short period of time should be avoided. Renal function should be reassessed after 24–48 hours. The use of biomarkers allows the detection of subclinical damage even before creatinine increases.

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