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Review Article

Research progress on risk factors and early predictors of contrast-induced nephropathy

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Abstract: As a serious iatrogenic complication, the incidence and clinical importance of contrast-induced nephropathy (CIN) have become increasingly prominent. CIN not only increases the length of hospital stay, medical cost and short-term mortality, but also is an independent predictor of long-term renal function deterioration and adverse cardiovascular events. At present, there is no effective method to completely avoid the occurrence of CIN after the use of contrast media in clinical practice, and the treatment of CIN that has occurred is also limited. Therefore, the prevention of CIN has become the focus of clinical research, and the identification of the risk factors of CIN is the basis and key link in the development of prevention programs. The purpose of this study is to review the existing evidence and further study the pathogenesis, risk factors and early predictors of CIN, so as to provide a reference for medical staff to formulate preventive measures, thereby reducing the risk of CIN and improving medical quality and ensuring patient safety.

Keywords: Contrast-induced nephropathy, pathogenesis, risk factors, early prediction, biomarkers

Introduction

With the rapid development of modern medical imaging and interventional therapy technology, contrast agents are increasingly widely used in cardiovascular, urinary, neurological and other fields [1]. However, the use of contrast agents is not without risks. As a serious iatrogenic complication, contrast-induced nephropathy (CIN) has gradually attracted high attention in the medical community [2]. CIN, also known as contrast agent-associated acute kidney injury, is a serious iatrogenic complication after intravascular injection of iodinated contrast agent. Its epidemiological characteristics and clinical harm are significant, and it is the third most common cause of hospital-acquired acute kidney injury (the incidence is second only to renal hypoperfusion and renal injury caused by nephrotoxic drugs) [3-5]. There are many influencing factors of CIN, which leads to limited heterogeneity in its incidence. For example, current studies show that CIN incidence is about 2% in the general population [5], in patients undergoing percutaneous coronary intervention (PCI), CIN incidence is about 7.1% [6], and in patients with abnormal renal function can be as high as 30%-40% [7].

In the short term, CIN significantly prolongs hospital stay, increases medical costs, and can lead to severe acute kidney injury requiring renal replacement therapy. More importantly, a large amount of evidence-based medical evidence has shown that the occurrence of CIN is a strong independent predictor of short-term and long-term mortality and major adverse cardiovascular events [8-10]. A study of 402 patients with CIN after primary PCI showed that in-hospital mortality was as high as 9.7%, and the risk of death was independently associated with right ventricular infarction, intraoperative arrhythmia and pump failure [6]. Even with the recovery of serum creatinine, about 25%-30% of patients will progress to chronic renal insufficiency and accelerate the evolution to end-stage renal disease [4]. At present, there is no effective method to completely avoid the occurrence of CIN after the use of contrast media in clinical practice, and the treatment for CIN is also limited. Therefore, the prevention of CIN has become the focus of clinical research, and

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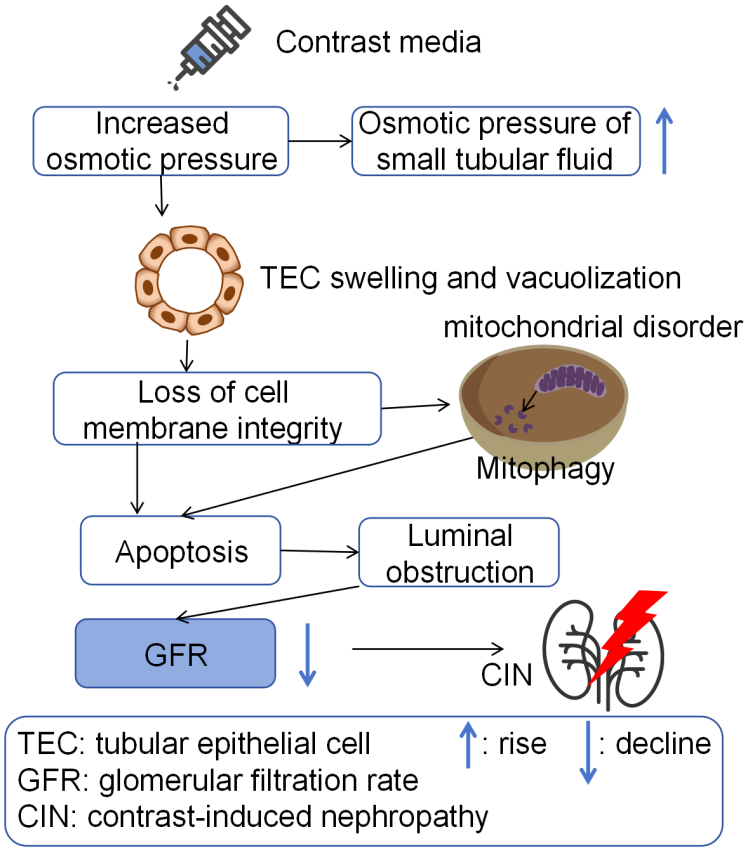

Figure 1. Direct toxic effects.

the identification of the risk factors of CIN is the basis and key link in the development of prevention programs.

The purpose of this study is to further study the pathogenesis, risk factors and early predictors of CIN, so as to provide a reference for medical staff to formulate preventive measures, thereby reducing the risk of CIN and improving medical quality and ensuring patient safety.

Major pathogenesis of CIN

Direct nephrotoxic effects

The direct toxic effect of contrast-induced nephropathy is mainly due to the immediate damage to renal tissue caused by the chemical and physical properties of iodinated contrast agents [11]. The contrast agent molecules (usually triiodobenzene ring derivatives) have high permeability. When they go through the renal tubules with blood flow, they are rapidly concentrated due to water reabsorption, resulting in a sharp increase in the osmotic pressure of the tubular fluid and causing osmotic nephropathy, which is manifested as swelling, vacuolization and destruction of the integrity of the cell membrane of the renal tubular epithelial cells [12]. The high viscosity of the contrast agent can cause red blood cells to accumulate in the renal tubules, hindering microcirculation and leading to ischemia and hypoxia in the outer medulla [13]. The chemical structure of contrast agents can also directly react with amino acids such as cysteine and tyrosine in cell membrane proteins, interfering with mitochondrial enzyme activity, causing energy metabolism disorders, intracellular calcium homeostasis disorders and DNA damage, and eventually inducing cell apoptosis [14]. Together, these direct toxic effects induce acute kidney injury through shedding of renal tubular epithelial cells, lumen obstruction, and a decrease in the glomerular filtration rate. The specific mechanism of direct nephrotoxic effects of contrast media is shown in **Figure 1**.

Recent studies have further deepened the understanding of the molecular mechanisms of direct nephrotoxicity. Acute oxidative stress and metabolic disorders induced by contrast media can specifically activate the programmed cell death pathway in renal tubular epithelial cells. The activation of ferroptosis is closely related to the abnormal accumulation of lipid peroxides caused by the depletion of glutathione and the inhibition of GPX4 activity. At the same time, damage signals can initiate the NLRP3 inflammasome dependent pyroptosis pathway, and cleave GSDMD protein through Caspase-1 to form plasma membrane holes, leading to cell lysis and the release of a large number of pro-inflammatory factors [15-17].

Indirect nephrotoxic effects

The indirect toxic effects of contrast-induced nephropathy mainly involve systemic and local

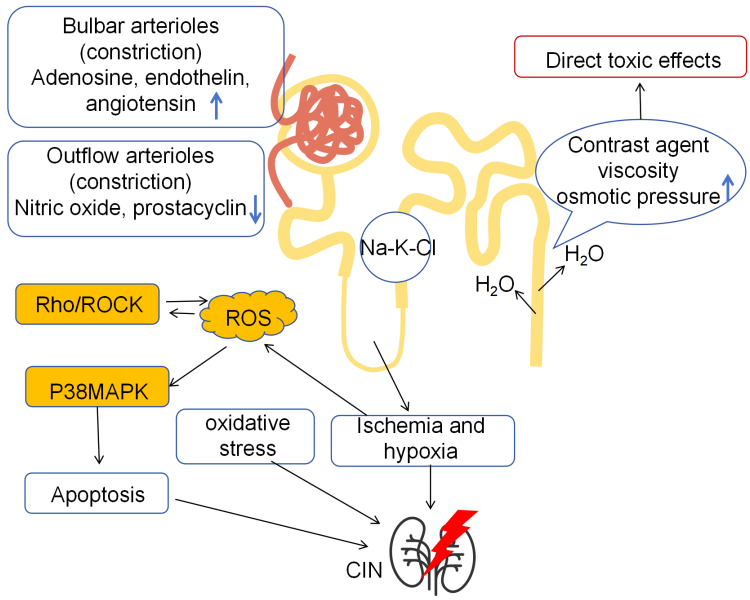

Figure 2. Indirect toxic effects.

physiological regulation abnormalities, leading to renal hemodynamic disorders and secondary injury. Intravascular injection of contrast material triggers a biphasic hemodynamic response [18, 19]: an initial transient renal vasodilatation is followed by sustained vasoconstriction accompanied by abnormal relaxation and contraction of the renal tubular system, leading to a significant reduction in renal blood flow and a decrease in glomerular filtration rate. This process is mainly attributed to the imbalance of vasoactive factors, that is, the release of contractile mediators (such as adenosine, endothelin and renin-angiotensin) is increased, while the production of diastolic mediators (such as nitric oxide and prostaglandin) is decreased, resulting in blood flow disorders in the peritubular capillaries and ischemia and hypoxia in the medulla [20]. Osmotic diuresis induced by contrast media can increase the burden of renal tubular reabsorption, further exacerbate medullary oxygen consumption, and activate "tubulobulb feedback" to further inhibit glomerular filtration [20]. The renal medulla itself is highly sensitive to ischemic injury due to low partial pressure of oxygen and active metabolism. This indirect hemodynamic disorder and hypoxia can further induce oxidative stress, inflammatory response and programmed cell death, eventually leading to acute renal function injury [20]. The specific mechanism of indirect nephrotoxic effects of contrast media is shown in **Figure 2**.

In conclusion, the pathogenesis of CIN is a network of multiple pathways. Direct nephrotoxicity results from immediate damage to the renal tubular epithelium caused by the physicochemical properties of the contrast agent. Indirect nephrotoxicity initiates injury by causing renal hemodynamic disturbance and medullary hypoxia. Recent studies have further clarified that oxidative stress and inflammation are the common hubs of the above two types of toxic effects, and their downstream effect can precisely activate new cell death programs such as ferroptosis and pyroptosis, and damage the mitochondrial quality control system. Understanding this complete chain, from macro initiation to micro execution, is fundamental to exploring targeted intervention strategies.

Risk factors of CIN

Basic renal insufficiency

Basic renal insufficiency is an important risk factor for CIN, which indicates that the same degree of contrast agent exposure may only cause reversible vasoconstriction in patients with normal renal function, but in patients with renal insufficiency, due to endothelial dysfunction and insufficient oxidative stress reserve, it may rapidly progress to irreversible cell apoptosis and inflammatory infiltration [21]. Li et al. [4] pointed out in their study that the renal reserve function of patients with renal insufficiency decreased and the ability to excrete the contrast agent weakened, resulting in the accumulation of contrast agent in the body, which significantly increased the risk of CIN. In a retrospective study of 16 institutions, Choi et al. [22] concluded that the risk of CIN in patients with chronic kidney disease was 1.215 times higher than that in patients without chronic kidney disease. The core mechanism by which basic renal insufficiency increases the risk of CIN is the remodeling of renal structure and function and

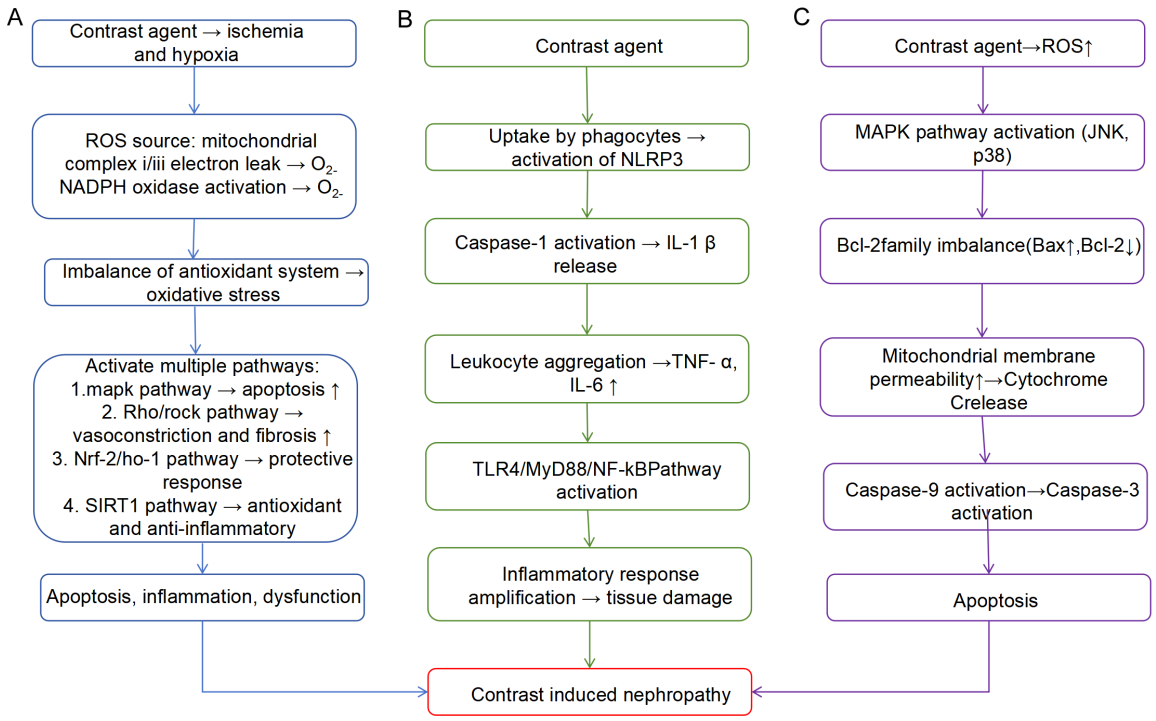

Figure 3. Core mechanisms by which underlying renal insufficiency increases the risk of developing CIN. CIN: contrast-induced nephropathy.

the depletion of compensatory reserve caused by chronic kidney disease, which makes the kidney more susceptible to multi-pathway damage cascades after contrast agent exposure.

The functional ability of nephrons in patients with chronic kidney disease is significantly reduced, the residual nephron functionality is in a state of compensatory hyperfiltration and hypermetabolism, and the mitochondrial energy demand of renal tubular epithelial cells is increased but the reserve capacity is decreased. This makes renal tubular cells more susceptible to mitochondrial dysfunction when exposed to contrast agents (**Figure 3** AC mechanism). Abnormal electron transport chain leads to the explosive production of reactive oxygen species (ROS), and the activity of antioxidant defense systems (such as Nrf2/HO-1 pathway) is impaired, and oxidative stress damage is aggravated [23]. Patients with renal insufficiency often have low-grade systemic inflammation, their monocyte-macrophage system is in a pre-activated state, and basal levels of local inflammatory mediators (such as IL-6 and TNF-α) in the kidney are increased. This makes it easier for the contrast agent to activate the NLRP3 inflammasome (**Figure 3** BE mechanism), plus the caspase-1-mediated maturation release process of IL-1β is amplified, and the inflammatory transcriptional activation of the TLR4/NF-κB signaling pathway is enhanced [24]. In the environment of chronic kidney injury, the expression of pro-apoptotic proteins (such as Bax) is increased, the expression of anti-apoptotic proteins (such as Bcl-2) is decreased, and the stability of the mitochondrial membrane is decreased in renal tubular epithelial cells. The increase in ROS induced by the contrast agent can directly activate the mitochondrial apoptotic pathway (**Figure 3** CF mechanism), and the threshold for cytochrome C release and caspase-9/3 activation is significantly reduced, resulting in a large increase in the proportion of apoptotic cells [25].

Diabetes mellitus

Diabetes mellitus, as one of the most common chronic diseases, is also an important risk factor for CIN. The results of Cetin et al. [26] showed that after the use of contrast agents, the risk of CIN in patients with diabetes was 1.711 times higher than that in patients without diabetes, and there may be an interaction between diabetes and gender, cardiac status,

and renal status of patients. The research results of Herath et al. [27] showed that among the various comorbidities of patients, diabetes had the most significant impact on the occurrence of CIN. The core mechanism by which diabetes increases the risk of CIN is the "additive effect" of multiple pathophysiological changes in a high glucose environment, which significantly reduces the renal defense ability against contrast medium damage.

High glucose persistently damages vascular endothelial cells, resulting in decreased synthesis and increased degradation of nitric oxide (NO), as well as up-regulation of endothelin-1 expression and excessive activation of the renin-angiotensin system (RAAS) [28]. This makes the renal vessels of diabetic nephropathy patients more sensitive to the vasoconstrictive effects (such as adenosine release and prostaglandin reduction) caused by contrast agents, and the decrease of renal blood flow and the degree of medullary hypoxia are significantly aggravated [29]. In the diabetic state, NADPH oxidase activity continues to increase, mitochondrial electron transport chain dysfunction is enhanced, and the basal level of ROS production increases [29]. After contrast agent exposure, the explosive increase of ROS is more likely to break through the damaged antioxidant defense system (such as the decreased activity of Nrf2/HO-1 pathway), leading to lipid peroxidation, DNA damage and abnormal protein function, which directly induces the death of renal tubular epithelial cells [28, 29]. Renal tubular epithelial cells highly express sodium-glucose cotransporter 2 (SGLT2). In diabetes, glucose reabsorption increases, energy consumption of active sodium transport increases, and oxygen demand increases significantly [30]. The reduction of renal blood flow caused by contrast media superimposed with high oxygen consumption led to a sharp drop in medullary oxygen partial pressure and abnormal activation of hypoxia-inducible factor (HIF-1α), which further promotes inflammatory and fibrotic responses [31]. High glucose environments can down-regulate the expression of Bcl-2 and up-regulate the level of Bax, which reduces the threshold of mitochondrial apoptosis. At the same time, GSDMD-mediated pyroptosis and ferroptosis related pathways (such as inhibition of GPX4 activity) are also more easily activated [32]. Under the stimulation of contrast media, multiple death programs such as apoptosis, pyroptosis and ferroptosis are more likely to be initiated synchronously in diabetic renal tubular cells [32]. The core mechanism by which diabetes increases the risk of CIN as shown in **Figure 4**.

Age

Advanced age is an important risk factor for CIN, and its increased risk results from the combination of age-related systemic physiological decline and structural renal changes (as shown in **Figure 5**). The study results of Shuka et al. [33] showed that the proportion of CIN in patients aged ≥65 years after PCI was 17.79%, and multivariate analysis confirmed that age ≥65 years was a risk factor for CIN. With increasing age, the volume of the kidney may gradually decrease, and the number of nephrons (including the number of glomeruli and tubules) also decreases [34]. Glomeruli are tiny structures in the kidney that filter waste products from the blood, renal tubules are responsible for reabsorption and secretion, as well as regulating water and electrolyte balance in the body [34]. During the aging process of the kidney, the glomerulus may undergo sclerosis, that is, the thickening of the glomerular basement membrane and the occlusion of glomerular capillary loops, and these changes will reduce the filtration efficiency of the kidney [34]. At the same time, the function of the renal tubules may also be affected, including decreased reabsorption capacity and decreased secretory function, which may lead to decreased urine concentration capacity and electrolyte dysregulation [35]. In addition, the vascular system of the kidney also changes with age, and the vascular wall may become stiff and the elasticity of the blood vessels is reduced, which will affect the blood supply of the kidney and subsequently affect its filtration and excretion function [36]. This conclusion was also confirmed by the results of Wang [37] and Gupta [38]. Aging of renal cells may also be manifested by decreased cell proliferation capacity, increased apoptosis, and decreased repair and regeneration capacity [35, 36]. Metabolically, the ability of the aging kidney to remove drugs and toxins may be reduced, which may affect dosage requirements and therapeutic efficacy of drugs, increasing the risk of drug accumulation and

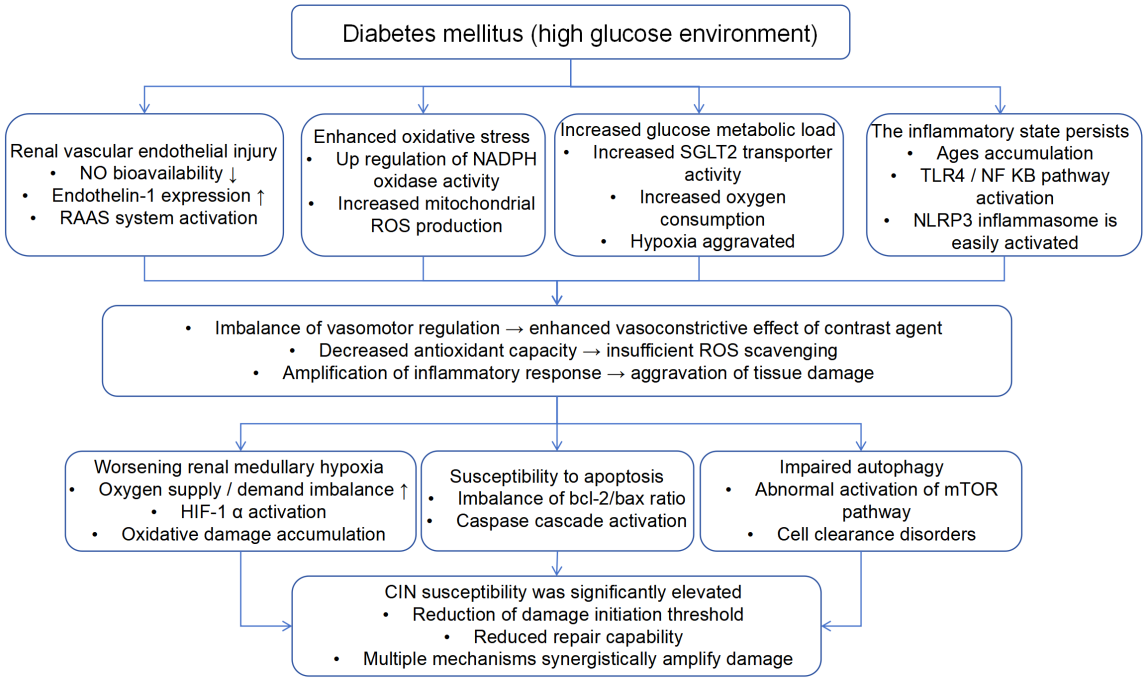

Figure 4. The core mechanism by which diabetes increases the risk of developing CIN. CIN: contrast-induced nephropathy.

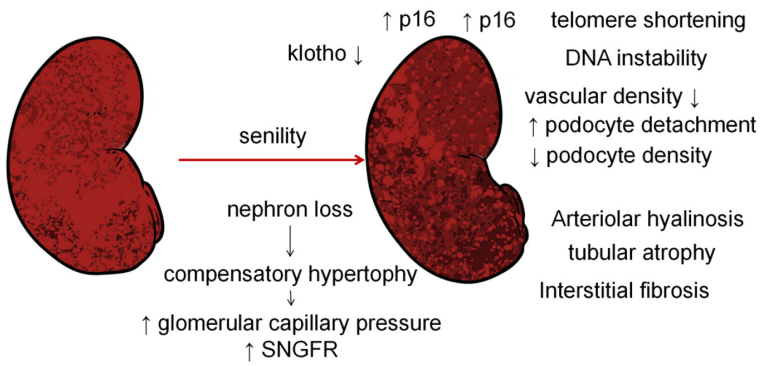

Figure 5. Functional and structural changes in aging kidneys.

toxic reactions [37, 38]. At the same time, the aging kidney may be more susceptible to pathological factors, such as chronic diseases such as diabetes and hypertension, which may accelerate the process of renal aging.

Other influencing factors

Clinically, in addition to the three core risk factors of basic renal insufficiency, diabetes, and advanced age, a variety of other clinical conditions (such as heart failure, contrast agent dose, and genetic factors) also significantly affect the risk of CIN (as shown in **Table 1**), and their mechanisms are mostly intertwined with known pathophysiological pathways. Patients with heart failure, especially those with NYHA class III-IV or those who have significantly reduced ejection fraction, have a significantly increased risk of developing CIN. This may be related to the fact that heart failure increases the risk of CIN and may be related to chronic renal hypoperfusion caused by decreased cardiac output, which in turn makes the kidney highly dependent on vasodilator substances such as prostaglandins to maintain filtration function [33, 39]. After contrast agent injection, the inherent vasoconstrictive effect of the body (mainly involving adenosine release and nitric oxide inhibition) produces an "additive effect" with the pre-existing renal vasoconstrictive background of heart failure, which can dramatically worsen renal medullary ischemia and hypoxia, and then increase the risk of CIN [40]. The contrast agent is completely filtered through the glomerulus and is not reabsorbed by the renal tubules. Increasing doses and concentrations

Table 1. Early biomarkers of contrast-induced nephropathy

Biomarkers	Cut-off	AUC	Sensitivity and specificity
Neutrophil gelatinase-associated lipocalin [42]	96.24 (ng/mL)	0.824	98.27% and 67.02%
Kidney injury molecule-1 [45]	9.49 (ng/mL)	0.887	80.00% and 81.70%
Liver-type fatty acid binding protein [48]	22.05 (μg/gCr)	0.740	63.60% and 71.40%
cystatin C [42]	1.12(mg/L)	0.753	61.78% and 92.38%

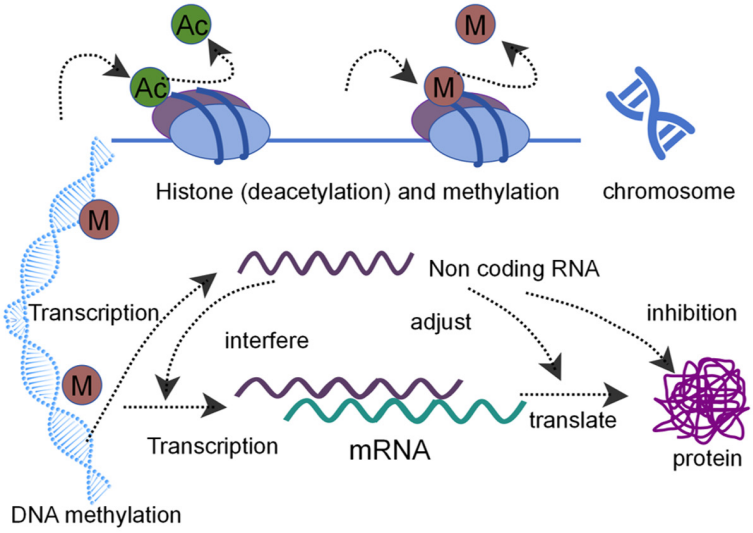

Figure 6. The core mechanism by which genetic factors increase the risk of developing CIN. CIN: contrast-induced nephropathy.

can prolong the renal exposure time. In this process, the concentration of contrast agent in the renal tubules continues to increase, and the viscosity increases exponentially, leading to the damage of renal tubular endothelial cells and the reduction of blood flow, which eventually leads to the apoptosis of renal tubular cells and renal function damage. Liao et al. [41] showed that there was a clear, quantifiable, and population-heterogeneous positive relationship between the dose of contrast media and the risk of CIN. Moreover, the increased dose of contrast media increased the risk of CIN even after adjusting for multiple confounding factors. In recent years, with the development of epigenetic research, the role of genetic factors in the occurrence and development of a variety of diseases has attracted wide attention. Genetic factors indirectly affect the susceptibility to CIN by setting an individual's epigenetic background and gene expression potential. Rather than being a direct, independent and strong risk factor like "diabetes", genetic factors are an important biological modifier that accounts for some of the individual differences that clinical risk models cannot capture (see **Figure 6**). Incorporating genetic and epigenetic information into future studies is a critical step toward truly personalized prevention of PC-AKI.

In summary, risk factors for CIN can be divided into non-modifiable factors (such as advanced age, underlying renal insufficiency, and diabetes) and variable or manageable factors according to their clinical intervenability. The former is the core basis for risk stratification, which is used to identify high-risk groups. In contrast, the latter, such as optimizing the volume given to patients with heart failure, precisely calculating and limiting the dose of contrast media according to renal function (with the use of formulas such as the ratio of contrast media dose to glomerular filtration rate), and withholding nephrotoxic medications, all provide direct and critical intervention targets for clinical prevention. Therefore, for high-risk patients, systematic evaluation and active management of these variables before imaging or intervention should be the core practice to reduce the incidence of CIN.

Early predictors of CIN

At present, the diagnosis of CIN is based on the change of Scr, but it is not ideal as an experimental diagnostic index reflecting early renal damage. Non-renal factors (such as gender, age, race, etc.) have an impact on Scr level. The normal reference value of Scr is relatively large and lacks specificity in monitoring the development and changes of the disease. Because the kidney has a strong reserve function, GFR

will not increase until it decreases by more than 50%, and Scr may not increase in some patients with severe nephropathy. Scr is usually elevated after 48 hours after renal injury, so it is not sensitive for early diagnosis of renal injury. At present, diagnostic delay has become the main obstacle to treatment. In the field of early warning research of CIN, the value of a single early predictor is that it can capture the initial pathophysiological changes in the kidney after contrast agent attack before SCr, which is a traditional diagnostic marker. These indicators mainly cover two categories: new biomarkers and functional imaging parameters, which reveal the early initiation of CIN from different levels. New biomarkers are the forefront and core of current research. Among them, the evidence of protein markers reflecting renal tubular injury and stress is the most sufficient.

Novel biomarkers

Neutrophil gelatinase-associated lipocalin (NGAL) is rapidly synthesized and released by renal tubular epithelial cells after ischemia or nephrotoxic injury. Its concentration in blood and urine can be significantly increased within 2-6 hours after injury. It has a high time sensitivity and is currently recognized as one of the most potential early warning molecules [42-44]. Luo et al. [45] pointed out in their study that NGAL level at 6 hours after surgery had an AUC of 0.824 for predicting CIN in PCI patients. Kidney injury molecule-1 (KIM-1) is a membrane-spreading protein located on the membrane of renal proximal tubular epithelial cells. It is almost not expressed in normal renal tissues, but when renal tissues are exposed to ischemia and hypoxia, the expression is significantly increased, and it is positively correlated with the degree of renal injury [46-48]. The KIM-1 shedding fragment can be detected in urine, although slightly later than NGAL, because it is directly related to the repair process of renal tubular injury, and the specificity is higher [46-48]. Previous studies [48] reported that the AUC of baseline serum KIM-1 concentration in predicting CIN in elderly patients with NSTEMI was as high as 0.887. The physiological significance of Liver-type fatty acid binding protein (L-FABP) is particularly unique, as it is mainly expressed in the proximal tubule and is highly sensitive to tissue hypoxia [49, 50]. Given that renal medullary hypoxia is one of the recognized core pathogenesis of CIN, the early elevation of L-FABP provides direct molecular evidence for this pathological process, making it a specific predictive tool for mechanism orientation [49-51]. Cystatin C (Cys-C) is produced by nucleated cells at a constant rate and reabsorbed in the proximal renal tubules [52, 53]. Cystatin C levels are less affected by muscle mass, age, sex, or nutritional status than serum creatinine and therefore more reliably predict the risk of worsening renal function [45, 52, 53].

Imaging parameters

Imaging parameters play an increasingly important role in the early prediction of CIN. By providing non-invasive, quantitative measures and being directly related to the pathophysiological mechanism of visual information, it utilizes dynamic capture and objective assessment of the early process of the disease. As a convenient bedside examination method, the predictive value of ultrasound Doppler Renal Resistance Index (RRI) derives from its immediate reflection of renal hemodynamic status [54]. RRI calculates a quantitative index reflecting intrarenal vascular resistance by measuring the peak systolic velocity and end-diastolic velocity of segmental or interlobar arteries [55]. Contrast agents can cause biphasic hemodynamic responses in renal vessels, especially secondary persistent vasoconstriction, which increases intrarenal arterial resistance and reduces diastolic blood flow, thereby causing an increase in RRI value [56]. A number of clinical studies have shown that in high-risk patients receiving contrast exposure, a significant increase in RRI (threshold is usually defined as >0.75) in the early postoperative period (e.g., within 24 hours) is positively correlated with the risk of subsequent CIN, and such hemodynamic changes usually precede the significant rise in serum creatinine [57-59]. Therefore, RRI is not only a predictive tool, but also a potential means of monitoring renal vascular response in real time and evaluating the effect of preventive interventions such as adequate hydration.

Blood oxygen level-dependent MRI (BOLD-MRI) provides more in-depth early warning information from the level of tissue oxygen metabolism

[60]. The principle of this technique is based on the paramagnetic properties of deoxyhemoglobin, whose R2 value (transverse relaxation rate) is inversely related to the local oxygen content of the tissue [61]. The kidney, especially the medulla, is in a relatively hypoxic environment under physiological conditions. Medullary hypoxia is further exacerbated by the contrast media-induced reduction in blood flow and increased oxygen demand, which increases the burden of tubular reabsorption due to osmotic diuresis. BOLD-MRI can noninvasively and quantitatively map the oxygenation profile of the whole kidney cortex and medulla [61]. Studies have confirmed that after the injection of contrast agent, the renal medullary R2 value of patients with future CIN will show an early and significant increase, indicating a decrease in medullary oxygenation, and this change can occur before abnormal renal function indicators [62]. This enables BOLD-MRI to "visualize" hypoxia in the core pathogenesis of CIN, which not only can be used for the screening of high-risk individuals, but also provides a unique research perspective for exploring the effects of different prevention strategies on improving renal medullary oxygenation.

In conclusion, the early prediction of CIN has entered the "post-creatinine era". New biomarkers represented by NGAL and KIM-1 and functional imaging parameters represented by renal resistance index can reflect renal injury earlier and more specifically. At the same time, the research paradigm is shifting from a single marker to multi-dimensional joint prediction models, especially machine learning models integrating high-dimensional data, which show higher prediction performance.

Prediction models

In recent years, with the deepening of biomarker research and the popularization of data analysis methods such as machine learning, the construction of CIN risk prediction models has shown a trend of development from single markers to multi-dimensional joint prediction, and from traditional regression to complex machine learning models. The joint prediction model significantly improves the risk identification ability by integrating different types of predictors. Its construction is mainly based on two directions: the first is the combination of clinical variables and new biomarkers. For example, in emergency PCI patients, a scoring model integrating eight indicators including female gender, stroke history, left ventricular ejection fraction, high endothelin-1 level, and estimated glomerular filtration rate showed good discrimination (C statistic = 0.787) [63]. More studies have combined biomarkers such as cystatin C (Cys-C) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) with traditional risk factors (such as age and diabetes) to further optimize the prediction performance [64]. The second direction is to apply machine learning algorithms to integrate high-dimensional data. A number of studies have confirmed that machine learning models such as support vector machine (SVM) and Random Forest can efficiently process more than a dozen clinical and biochemical variables, including uric acid, cystatin C, creatine kinase isoenzyme, systemic immune inflammation index, and so on. The area under the prediction curve (AUC) can reach 0.784-0.82. It is superior to the traditional logistic regression model [64, 65]. These algorithms can not only mine the nonlinear relationship, but also explain the contribution of each variable through the ranking of feature importance (such as SHAP value), which enhances the interpretability of the model [64]. Despite the fruitful research results of predictive models, their translation into routine clinical application still faces the challenges of insufficient model universality and validation: Most models are derived from single-center, retrospective data, and lack of external validation in different populations, different contrast agent types (such as gadolinum-based contrast agent), or different surgical scenarios (such as elective PCI, emergency PCI, or peripheral vascular intervention), which limits their wide applicability [66]. Successful future translation depends on the model being validated in a multicenter prospective cohort and developed as a decision support tool for easy clinical use, thus truly enabling a closed loop from risk identification to preventive action.

Conclusion

CIN is an important iatrogenic complication in clinical practice, and its mechanism is complex, involving the interaction of multiple pathways such as direct nephrotoxicity, hemodynamic disturbance, oxidative stress and inflammatory

activation. This review focuses on the pathogenesis and early predictors of CIN, aiming to lay the foundation for risk warning and the development of mechanism-based precise prevention strategies in the future. Basic renal insufficiency, diabetes and advanced age are the core risk factors of CIN, while heart failure and high dose of contrast agent also significantly increase the risk of CIN. At present, the early prediction of CIN has shifted from relying on serum creatinine to the application of new biomarkers (such as NGAL and KIM-1) and functional imaging indicators (such as renal resistance index), which can indicate renal injury earlier. Future research should focus on integrating dynamic biomarkers and clinical data, constructing individualized prediction models, and exploring precise prevention strategies for specific injury pathways. In addition, with the development of high-throughput technology and multi-omics analysis, single-cell sequencing is expected to reveal the specific responses of renal cell types and intercellular communication networks during CIN. Liquid biopsy (such as circulating cell-free DNA and exosomes) can provide a new window for non-invasive monitoring of renal injury and repair dynamics. Renal function imaging genomics may achieve earlier risk identification and mechanism analysis by fusing imaging features and genetic information. In the future, based on the in-depth understanding of the above molecular mechanisms and early warning signals, the prevention strategy of CIN is expected to shift from universal hydration and drug intervention to targeted intervention of specific damage pathways, such as NLRP3-mediated pyroptosis or ferroptosis, so as to achieve truly individualized prevention.

Disclosure of conflict of interest

None.

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