Contrast-induced nephropathy; an update on pathophysiology

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Abstract
Contrast-induced nephropathy (CIN) is a well-known complication of contrast media administration for diagnostic and therapeutic purposes. The incidence of CIN has increased with the widespread use of diagnostic imaging and contrast media. CIN is a pathological condition that typically occurs within 48 hours of exposure to contrast material and results in an increase in serum creatinine levels of more than 44 µmol/L (0.5 mg/dL) or 25% above baseline or an increase in serum creatinine of more than 1.5 times the baseline level within 7 days of exposure to contrast material or a reduction in urine output to less than 0.5 mL/h for at least 6 hours after exposure to contrast material. The mechanism of CIN is not fully understood, but it is thought to involve direct nephrotoxic effects of contrast particles, hemodynamic changes, hypoxia and oxidative stress, apoptosis, inflammation, and immune responses. Prevention of CIN involves identifying the risk factors and taking appropriate measures to mitigate them. Currently, there is no definitive treatment for CIN, and treatment is mainly symptomatic, with supportive care being the mainstay. Experimental treatments such as renal replacement therapy, extracorporeal blood purification, and stem cell therapy are being investigated, but their clinical efficacy is yet to be established.

Keywords: Contrast-induced nephropathy, Glomerular filtration rate, Acute tubular necrosis, Iodine-containing contrast media, Reactive oxygen species, Apoptosis, Oxidative stress, Serum creatinine


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Introduction
The administration of contrast agents in clinical imaging has significantly increased with the advent of advanced imaging technology, resulting in a higher incidence of adverse effects associated with exposure to contrast particles, such as contrast-induced nephropathy (CIN) (1). The first reported case of CIN occurred in 1954 when Bartels described a case of anuria following intravenous pyelography (2). CIN is a pathological condition that usually manifests 48 hours after exposure to a contrast agent, resulting in an increase in serum creatinine level by more than 2.44 µmol/lit (or 0.5 mg/dl or 25%) compared to the baseline level (1). Other diagnostic criteria include an increase in serum creatinine level by more than 1.5 times the baseline level during seven days after exposure to a contrast agent or a decrease in urinary output to less than 0.5 ml/h for at least six hours after exposure to a contrast agent (3). CIN is currently the third leading cause of acute kidney injury (AKI) (4). The incidence of CIN in the general population is 1-2% (5), and its incidence has been reported in 1-25% of cases of hospital-acquired AKI (6). Although CIN can be reversible, 15% of patients with CIN temporarily require dialysis (7).

Based on the distribution of creatinine in the body fluids, a slight increase in creatinine level occurs after the injection of a contrast agent following a decrease in glomerular filtration rate (8). Plasma creatinine levels are influenced by factors such as muscle mass, age, gender, and body hydration status, and therefore, the sensitivity and specificity of creatinine for diagnosing CIN are low (9, 10). Biomarkers with higher sensitivity and specificity for evaluating CIN have been identified, including cystatin-C, neutrophil gelatinase-associated lipocalin-liver type fatty acid-binding protein, and kidney injury molecule-1 (11).

Study method
This review collected materials through a search of international databases such as PubMed to obtain relevant information. The keywords of contrast-induced nephropathy, acute tubular necrosis, iodine-containing contrast media, reactive oxygen species, apoptosis, glomerular filtration rate, oxidative stress and serum creatinine were used to retrieve the relevant articles.

Prevention of contrast-induced nephropathy
Prevention of CIN is crucial as there is no definitive
treatment for it. Risk factors for CIN can be classified into two categories; patient-related factors and procedure-related factors. Patient-related factors include diabetes mellitus, renal dysfunction, decreased effective volume within vessels, old age, female gender, cardiovascular diseases, cancer, inflammation, anemia, and the use of nephrotoxic drugs and antiviral drugs. Procedure-related factors include the site of contrast material injection, arterial or venous injection, type of contrast material, the volume of contrast material administered, and the number of contrast material injections within the first 24-72 hours (12).

There is no specific treatment for acute tubular necrosis caused by contrast material. Symptomatic treatment includes correction of hydration status and hydration of the patient with normal saline or bicarbonate or both, administration of N-acetylcysteine, discontinuation of nephrotoxic drugs, and administration of drugs such as angiotensin receptor blockers, statins, ascorbic acid, and theophylline. Although hemodialysis and hemofiltration can remove contrast material, prophylactic hemodialysis has no effect on the occurrence of AKI and complications caused by contrast material (13-15).

Pathophysiology of CIN
The pathophysiology of CIN is multifactorial and involves various mechanisms, including direct nephrotoxic effects of contrast particles, hemodynamic changes, hypoxia and oxidative stress, apoptosis, inflammation, and immune response (16). Iodine-containing contrast media (ICM) contain radiopaque iodine atoms that are placed on watersoluble carbon molecules. The osmolality of contrast materials used has decreased over time, leading to a significant reduction in the occurrence of AKI due to their use (17). After intravenous injection of contrast agents, various hemodynamic changes occur in the kidneys. One of the most important of these is rapid and temporary vascular dilation, followed by stable vasoconstriction. In addition to vasoconstriction of the afferent and efferent arterioles of the kidneys, their sensitivity and response to angiotensin-2, which is one of the most fundamental vasoconstrictors, increases, and this exacerbates vascular constriction (18-20).

Experimental findings show that the injection of iodinated contrast agents causes hypoxia and the formation of reactive oxygen species (ROS) in the kidney, which has a key role in CIN. Following the injection of the contrast agent and tubular vasoconstriction, oxygen delivery to the kidneys decreases, and a decrease in the tissue oxygen level of up to 10mmHg has been reported by oxygen microelectrodes. To combat insufficient oxygen levels, nitric oxide and prostaglandins are released to improve tissue oxygenation by increasing peripheral blood flow. However, the cytotoxic effects of contrast particles on endothelial cells lead to increased endothelin and adenosine levels, and decreased nitric oxide (NO) and prostaglandins. With continued changes, hypoxia and ischemia can occur. Another cause of medullary hypoxia is the increased oxygen consumption following the transport of contrast material through tubules, which is associated with changes in renal microcirculation. (21,22).

The increase in oxygen consumption following the transport of contrast materials is associated with changes in renal microcirculation. Contrast media agents are diuretics and cause an increase in energy consumption in the ascending limb of Henle's loop. In fact, oxidative stress plays a role in all mechanisms that lead to CIN. Hypoxia leads to a deficiency in oxidative phosphorylation and increases the production of free radicals in the mitochondria. The cytotoxic effect of contrast particles on renal tubular cells causes mitochondrial damage, endoplasmic reticulum stress, and plasma membrane damage (20). Mitochondrial membrane damage leads to the release of significant amounts of ROS. Endoplasmic reticulum stress leads to cytosolic calcium overload, which plays a key role in the production of ROS. The production of ROS is strongly related to the progression of CIN and directly damages renal tubular cells. In addition, by activating stress kinases such as p38 MASK Stress kinases and caspases, ROS can cause apoptosis of renal cells. Moreover, ROS and superoxide anions react with nitric oxide to produce peroxynitrite, which in turn causes significant damage to kidney cells. The most common types of ROS include superoxide, hydroxyl radicals, and hydrogen peroxide, which cause damage to proteins, nucleic acids, and cellular membranes. ROS-reducing drugs such as allopurinol can prevent a decrease in glomerular filtration rate (16, 23). Studies also show that reducing the formation of ROS following the administration of N-Acetyl cysteine and infusion of bicarbonate has a protective effect against CIN (21).

The contrast agent has specific physicochemical properties and is eliminated through glomerular filtration. Therefore, it may affect the diffusion of water molecules in the kidney. Jost et al measured the relationship between the viscosity of the contrast agent and the apparent diffusion coefficient of water using the phantom method. They found a significant difference in the apparent diffusion coefficient of the kidney between the injection of a hypotonic-saline contrast agent and an iso-osmolar contrast agent. Laboratory findings showed that the iso-
Contrast-agent-induced nephropathy

Contrast-induced nephropathy (CIN) is caused by the administration of contrast agents, which are commonly used in medical imaging procedures to enhance visibility of internal structures. The immediate effect of contrast agents is not only an increase in renal blood flow and glomerular filtration rate (GFR) but also an increase in renal interstitial pressure and vascular resistance, leading to transient ischemia and nephrotoxicity. The long-term consequences of CIN include chronic kidney disease (CKD) and cardiovascular events. Therefore, understanding the mechanisms that contribute to kidney cell damage and the development of effective preventive strategies is critical.

**Mechanisms of CIN**

The mechanisms of CIN are multifactorial, involving both direct and indirect effects. Direct effects include the transport of contrast agents to perivascular phagocytes, leukocyte activity, and the activation of NLRP3 inflammasomes and interleukin-1-β (IL-1β). Indirect effects include oxidative stress, hypoxia, and mitochondrial depolarization, leading to the release of cytochrome C and the initiation of apoptosis of renal cells. Autophagy, a protective intracellular mechanism, may disrupt kidney function in CIN (26).

**Contrast injection**

Contrast injection leads to the release of inflammatory mediators such as interleukin-6 and tumor necrosis factor α (TNFα). Inflammatory mediators are thrombogenic. Interleukin 6 (IL-6) induces C-reactive protein (CRP) as an acute-phase reactant. If vasoconstriction accompanies inflammation and thrombogenic conditions, renal perfusion decreases and kidney damage occurs (24). Kwasa and colleagues demonstrated in 2014 that the incidence of contrast nephropathy in patients with CRP >5 mg/L was 13.5%, while it was 6.25% in patients with CRP ≤ 5 mg/L (27).

Recently Lau et al investigated the cellular and molecular mechanisms of nephropathy caused by contrast agents and showed that kidney damage is the result of the interplay between immune system effects, tubular epithelium, and leukocyte activity. This process involves the uptake and transfer of contrast agents to perivascular phagocytes, activation of NLRP3 inflammasomes and interleukin-1-associated leukocytes, renal DPEP-1-mediated contrast reabsorption, and ultimately, tubular cell injury. They emphasized the importance of the immune response in the CIN process and expressed that all of these processes are involved in the occurrence of nephropathy (28).

**Conclusion**

Contrast agents play an important role in medical imaging procedures; however, they can potentially have adverse effects on kidney function. These effects are attributed to various factors, including cytotoxicity, alterations in hemodynamic conditions, hypoxia and oxidative stress, apoptosis of renal cells, across with the initiation of an inflammatory response. As a result, these factors can contribute to kidney cell damage, constriction of renal blood vessels, a reduction in the glomerular filtration rate. Depending on the severity of the damage, contrast agent-induced nephropathy can be either reversible or irreversible.

**Authors' contribution**

Conceptualization: YYF, RM
Validation: YYF, RM, SS
Investigation: YYF, RM, SS
Resources: YYF, RM
Data curation: YYF, RM
Writing—original draft: YYF, RM
Writing—review and editing: SS
Visualization: SS
Supervision: SS

**Conflicts of interest**

The authors declare that they have no competing interests.

**Ethical issues**

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**References**

11. D’Amore C, Nuzzo S, Briguori C. Biomarkers of contrast-
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