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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

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Implication for health policy/practice/research/ medical education

Contrast-induced nephropathy is a pathological condition that usually manifests 48 hours after exposure to a contrast agent. This nephropathy is currently the third leading cause of acute kidney injury. Although contrast-induced nephropathy can be reversible, 15% of patients with this condition temporarily require dialysis.

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 water-soluble 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-

osmolar contrast agent caused a decrease in ADC due to its high viscosity. This justifies the delayed removal of iodine after the injection of an iso-osmolar contrast agent and demonstrates the importance of the physicochemical properties of contrast agents during renal filtration (24). Contrast particles can lead to a reduction in renal blood flow and the occurrence of CIN as a result of micro-embolism, as viscosity and osmolality of blood increase (24, 25).

Autophagy is an intracellular mechanism that removes damaged organelles and aggregated proteins to maintain cellular homeostasis. Autophagy is a protective mechanism in contrast nephropathy. The effect of autophagy on kidney injury is contradictory, and few studies have been conducted on its protective effect against stress. Ko et al demonstrated that oxidative stress caused by iohexol injection leads to mitochondrial membrane depolarization and cytochrome C release into the cytosol. Cellular stress related to oxidative stress and mitochondrial depolarization is closely related to autophagy. Autophagy is a mechanism that cooperates in nephropathy resulting from the contrast to combat stressful conditions and increase apoptosis and inflammatory cells. Its inhibition disrupts kidney function in CIN (26).

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

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Section 4: Contrast-induced AKI. Kidney Int Suppl. 2012;2:69-88. doi: 10.1038/kisup.2011.34. PMID: 25018920; PMCID: PMC4089629.
2. Luk L, Steinman J, Newhouse JH. Intravenous Contrast-Induced Nephropathy-The Rise and Fall of a Threatening Idea. Adv Chronic Kidney Dis. 2017;24:169-175. doi: 10.1053/j.ackd.2017.03.001.
3. Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158:825-30. doi: 10.7326/0003-4819-158-11-201306040-00007.
4. Katzberg RW, Haller C. Contrast-induced nephrotoxicity: clinical landscape. Kidney Int Suppl. 2006;(100):S3-7. doi: 10.1038/sj.ki.5000366.
5. Pflueger A, Abramowitz D, Calvin AD. Role of oxidative stress in contrast-induced acute kidney injury in diabetes mellitus. Med Sci Monit. 2009;15:RA125-36.
6. Pattharanitima P, Tasanarong A. Pharmacological strategies to prevent contrast-induced acute kidney injury. Biomed Res Int. 2014;2014:236930. doi: 10.1155/2014/236930.
7. Mohammed NM, Mahfouz A, Achkar K, Rafie IM, Hajar R. Contrast-induced Nephropathy. Heart Views. 2013;14:106-16. doi: 10.4103/1995-705X.125926.
8. Shams E, Mayrovitz HN. Contrast-Induced Nephropathy: A Review of Mechanisms and Risks. Cureus. 2021;13:e14842. doi: 10.7759/cureus.14842.
9. Kane-Gill SL, Meersch M, Bell M. Biomarker-guided management of acute kidney injury. Curr Opin Crit Care. 2020;26:556-562. doi: 10.1097/MCC.0000000000000777.
10. Zdziechowska M, Gluba-Brzózka A, Franczyk B, Rysz J. Biochemical Markers in the Prediction of Contrast-induced Acute Kidney Injury. Curr Med Chem. 2021;28:1234-50. doi: 10.2174/0929867327666200502015749.
11. D'Amore C, Nuzzo S, Briguori C. Biomarkers of contrast-

induced nephropathy: which ones are clinically important? Interv Cardiol Clin. 2020;9:335-344. doi: 10.1016/j.iccl.2020.02.004.
12. Cho E, Ko GJ. The Pathophysiology and the Management of Radiocontrast-Induced Nephropathy. Diagnostics (Basel). 2022 2;12:180. doi: 10.3390/diagnostics12010180.
13. Deray G. Dialysis and iodinated contrast media. Kidney Int Suppl. 2006;(100):S25-9. doi: 10.1038/sj.ki.5000371. PMID: 16612397.
14. Lehnert T, Keller E, Gondolf K, Schäffner T, Pavenstädt H, Schollmeyer P. Effect of haemodialysis after contrast medium administration in patients with renal insufficiency. Nephrol Dial Transplant. 1998;13:358-62. doi: 10.1093/oxfordjournals.ndt.a027830.
15. Vogt B, Ferrari P, Schönholzer C, Marti HP, Mohaupt M, Wiederkehr M, et al. Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. Am J Med. 2001;111:692-8. doi: 10.1016/s0002-9343(01)00983-4.
16. Zhang F, Lu Z, Wang F. Advances in the pathogenesis and prevention of contrast-induced nephropathy. Life Sci. 2020;259:118379. doi: 10.1016/j.lfs.2020.118379.
17. McCullough PA. Radiocontrast-induced acute kidney injury. Nephron Physiol. 2008;109:p61-72. doi: 10.1159/000142938.
18. Heyman SN, Rosen S, Rosenberger C. Renal parenchymal hypoxia, hypoxia adaptation, and the pathogenesis of radiocontrast nephropathy. Clin J Am Soc Nephrol. 2008;3:288-96. doi: 10.2215/CJN.02600607.
19. Liu ZZ, Viegas VU, Perlewitz A, Lai EY, Persson PB, Patzak A, et al. Iodinated contrast media differentially affect afferent and efferent arteriolar tone and reactivity in mice: a possible explanation for reduced glomerular filtration rate. Radiology. 2012;265:762-71. doi: 10.1148/radiol.12120044.
20. Scharnweber T, Alhilali L, Fakhran S. Contrast-induced acute kidney injury: pathophysiology, manifestations, prevention, and management. Magn Reson Imaging Clin N Am. 2017;25:743-753. doi: 10.1016/j.mric.2017.06.012.
21. Heyman SN, Rosen S, Khamaisi M, Idée JM, Rosenberger C. Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy. Invest Radiol. 2010;45:188-95. doi: 10.1097/RLI.0b013e3181d2eed8.
22. Heyman SN, Brezis M, Epstein FH, Spokes K, Silva P, Rosen S. Early renal medullary hypoxic injury from radiocontrast and indomethacin. Kidney Int. 1991;40:632-42. doi: 10.1038/ki.1991.255.
23. Zhao W, Swanson SA, Ye J, Li X, Shelton JM, Zhang W, et al. Reactive oxygen species impair sympathetic vasoregulation in skeletal muscle in angiotensin II-dependent hypertension. Hypertension. 2006;48:637-43. doi: 10.1161/01.HYP.0000240347.51386.ea.
24. Jost G, Lenhard DC, Sieber MA, Lengsfeld P, Hütter J, Pietsch H. Changes of renal water diffusion coefficient after application of iodinated contrast agents: effect of viscosity. Invest Radiol. 2011;46:796-800. doi: 10.1097/RLI.0b013e31822b1272.
25. Mehran R, Dangas GD, Weisbord SD. Contrast-Associated Acute Kidney Injury. N Engl J Med. 2019;380:2146-55. doi: 10.1056/NEJMra1805256.
26. Ko GJ, Bae SY, Hong YA, Pyo HJ, Kwon YJ. Radiocontrast-induced nephropathy is attenuated by autophagy through regulation of apoptosis and inflammation. Hum Exp Toxicol. 2016;35:724-36. doi: 10.1177/0960327115604198.
27. Kwasa EA, Vinayak S, Armstrong R. The role of inflammation in contrast-induced nephropathy. Br J Radiol. 2014;87:20130738. doi: 10.1259/bjr.20130738.
28. Lau A, Chung H, Komada T, Platnich JM, Sandall CF, Choudhury SR, et al. Renal immune surveillance and dipeptidase-1 contribute to contrast-induced acute kidney injury. J Clin Invest. 2018;128:2894-2913. doi: 10.1172/JCI96640.