Review article

The molecular mechanism of contrast-induced nephropathy (CIN) and its link to in vitro studies on iodinated contrast media (CM)

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Received 30th of October, 2017    Accepted 7th of November, 2017
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ABSTRACT

Iodinated contrast media (iodinated CM) have increased ability to absorb x-rays and to visualize structures that normally are impossible to observe in a radiological examination. The use of iodinated CM may destroy renal function, commonly known as contrast-induced nephropathy (CIN), which can result in acute renal failure (ARF). This review article mainly focuses on the following areas: (1) classifications of iodinated CM: ionic or non-ionic, high-osmolarity contrast media (HOCM), low-osmolarity contrast media (LOCM) and iso-osmolarity contrast media (IOCM); (2) an introduction to the physical and chemical properties of the non-ionic iodinated CM; (3) the management of anaphylactic reaction by iodinated CM; (4) a suggested single injection of adult doses and maximum dose for non-ionic iodinated CM; (5) the molecular mechanism of contrast-induced nephropathy (CIN); (6) In vitro studies on iodinated CM. Based on above information, this review article provide an insight for understanding the drug safety of iodinated CM.

1. Introduction

Iodinated contrast media (iodinated CM) absorb x-rays and visualize structures that are normally hard to observe in a radiological examination [1–4]. It has been used widely for many years. Contrast media provide an ability to enhance normal structures or pathological lesions, which makes these places look different from surrounding. The mechanism of iodinated contrast media is based on shielding effect: high energy x-ray penetrates substances and yields a dark place in a plane image. Iodine, the content of iodinated contrast media, absorbs the energy of x-ray; that is to say, iodinated CM “shield” x-ray from detector and lead to a high density, white “shadow” appearing. Iodinated CM elevate the sensitivity and diagnostic accuracy in radiological examination.

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with high risk of adverse drug reactions (ADR) and renal toxicity. Since the late 1960s, the nonionic low-osmolar contrast media (LOCM) have been developed to better safety and replace ionic iodinated CM for clinical uses. In 1996, the US Food and Drug Administration (FDA) approved the iso-osmolar contrast media (IOCM), iodixanol (Visipaque®), to have a better safety profile [14]. Furthermore, discomfort such as pain and heat associated with the injection site was found to be lower when using iso-osmolarity contrast media (IOCM) than low osmolar contrast media (LOCM) [14]. It is low neuro-toxicity and low osmolality that are important to intrathecal route injected contrast media, such as Iopamidol (Iopamiro®) 300 and Iohexol (Omnipaque®) 300 [16, 17]. Table 1 shows the biologic adverse drug reaction (ADR) difference between ionic iodinated CM and non-ionic iodinated CM. Currently used non-ionic iodinated CM in Taiwan and their chemical properties are summarized in Table 2. The chemical structures of non-ionic iodinated CM are shown in Fig. 2 [3, 11, 18-31]. In Table 3, we summarized the suggested single injection of adult doses and maximum dose for non-ionic iodinated CM by intra-arterial route. In Table 4, we summarized the suggested single injection of adult doses and maximum dose for non-ionic

| Ionization | Ionic | Non-ionic |
|-----------|-------|----------|
| Monomers  | ![Ionic Monomer](image1) | ![Non-ionic Monomer](image2) |
| Example   | Diatrizoate (Hypaque®) lothalamate (Conray®) | Iopamidol (Iopamiro®) Iopromide (Ultravist®) Iohexol (Omnipaque®) Ioversol (Optiray®) Iobitridol (Xenetix®) |
| Dimers    | ![Ionic Dimer](image3) | ![Non-ionic Dimer](image4) |
| Example   | Ioxaglate (Hexabrix®) Iodixanol (Visipaque®) |

Fig. 1 - Water-soluble iodinated CM are divided into four groups based on the structure. They are ionic monomer, ionic dimer, nonionic monomer and nonionic dimer.

Table 1 – The biologic adverse reaction between ionic and non-ionic contrast media.

| Biologic adverse reaction | Ionic contrast media | Non-ionic contrast media |
|--------------------------|----------------------|-------------------------|
| Thermal effect           | Moderate             | Mild to less             |
| Pain during injection    | Moderate             | Mild to less             |
| Nausea and vomiting      | Moderate             | Mild to less             |
| Toxicity to kidney       | Higher               | Lower                    |
| Tissue necrosis when extravasation occurs | More severe | Less severe |
| Other allergic effects    | Often (around 10%)   | Seldom (lower than 5%)   |
iodinated CM by intravenous route. In Table 5, we summarized the suggested single injection of adult doses and maximum dose for non-ionic iodinated CM by intrathecal route.

### 2. The adverse drug reaction (ADR) of iodinated contrast media and management

ADR caused by iodinated CM includes chemical and constitutional effects. Chemical effects are mainly referred as contrast-induced nephropathy (CIN) and will be discussed later. Anaphylactic reaction is the most common situation in constitutional effect and may cause mild symptom such as nausea and vomiting, dizziness, rash and itch, or chest discomfort, shock in more severe situation, or even death [21, 23, 28, 29, 32]. Iodinated contrast media cause little allergic reactions, especially for low-osmolar contrast media (LOCM). The incidence of adverse effect to LOCM is 2 to 7/1000, that of severe allergic reaction to LOCM is lower 1 to 4/100,000, and that of lethal rate to LOCM is around 2-9/1000,000 [33, 34]. We should recognize adverse effects and receive early intervene to reverse bad situation. The management and treatment of adverse effects on anaphylactic reaction by iodinated CM is proposed in 2017 RSROC Contrast Media Manual [33]. There are several affecting factors for anaphylactic reaction by iodinated CM such as particularly allergy (arising from consuming sea foods or drugs), previous adverse reactions, history of asthma or bronchospasm, history of allergy, cardiac disease, dehydration, haematological and metabolic conditions (sickle cell anaemia, patients with thrombotic tendency), renal disease, neoplasms, old patients, anxiety and apprehension medications (β-blockers, interleukin-2 (IL-2), aspirin, NSAIDs) [33]. In addition, IOCM (ie, iodixanol (Visipaque®)) are associated with the highest risk of causing a delayed hypersensitivity reactions. The incidence of delayed hypersensitivity reactions to IOCM is 10.9% and 5%-6% for LOCM [33, 35, 36]. Lasser et al. suggested that two doses of corticosteroid prophylaxis (32 mg of methyl prednisolone, orally 12 and 24 h before iodinated CM injection signification reduced the iodinated CM-induce anaphylactic reaction [13, 34].

### 3. Molecular mechanism of contrast-induced nephropathy (CIN)

CIN is one of chemical adverse effects of iodinated CM. The pathophysiology of CIN is related to hemodynamic changes caused by vasoconstriction which makes a decrease of glomerular filtration rate (GFR) and a renal ischemia. Direct cytotoxic-
Fig. 2 - The chemical structures of currently used non-ionic iodinated CM.

4. *In-vitro* studies on contrast-induced nephropathy (CIN) by iodinated CM.

In 2017 year, Charalampos Mamoulakis et al. summarize recent *in vitro* studies on oxidative stress related to CIN in animal models and humans [6]. Hereby, we summarize recent *in vitro* studies on the mechanisms in contrast-induced nephropathy (CIN). Direct damage, a risk factor of CIN, induces cell death to renal tubular cells caused by iodinated CM. Table 6 is a summary of the manifestation of CIN which is collected from *in vitro* studies. Inhibiting cell proliferation and inducing cell death are found in renal cell lines including KRK52-E, LLC-PK1, HKCS, HK-2 at the concentration higher than 75 mg/I/ml. Importantly, iodinated CM induced cell death no matter whether in LOC or IOCM. Apoptosis and/or autophagy are two cell types in cell death [52-58]. Readers refer to our previous article for detailed molecular mechanisms of apoptosis and autophagy [59].

5. Conclusion

Autophagy and apoptosis were associated with the pathophysiology of CIN in *in vitro* reports. In conclusion, *in vitro* studies showed that increased cell death by apoptosis and/or autophagy was demonstrated in the kidney cell lines after the administration of iodinated CM. Inhibition of autophagy induced cell apoptosis suggested the protective role of autophagy in CIN. In the future, studies about how to reduce cellular stress and cell death by new methods or new compounds and understanding the details molecular mechanisms may be helpful for the development of new therapeutic strategies for the treatment of CIN.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
### Table 3 – Suggested single injection of adult doses and maximum total dose for non-ionic contrast media by intra-arterial injection [31].

| Non-ionic contrast media | Angiography of arteries of extremity | Femoral arteriography | Aortography | Arteriography | Arteriography of cerebral arteries | Cardiac ventriculography, Left (FDA Dosage) | Cardiac ventriculography, Left (Off label Dosage) | Coronary angiography | Coronary angiography (Off label Dosage) | Inferior vena cavaogram |
|--------------------------|--------------------------------------|-----------------------|-------------|---------------|-----------------------------------|---------------------------------------------|-----------------------------------------------|---------------------|-------------------------------|------------------------|
| Iopromide (Ultravist) (300 mgI/ml) | 5-40 ml for subclavian or femoral artery | 25-50 ml for aortic bifurcation | 65 ml | 3-12 ml for carotid arteries | 4-12 ml for vertebral arteries | 20 to 50 ml for aortic arch injection | Blood flow and vascular and pathological nature of the vessels of interest | 30-60 ml | 44-60 ml | 7 to 10 ml (4-5 injections) left coronary artery | 7-10 ml (2 to 3 injections) right coronary artery |
| Maximum dose | 250 ml | 150 ml | |
| Iopromide (Ultravist) (370 mgI/ml) | Adult doses suggestion | Adult doses suggestion | Blood flow and vascular and pathological nature of the vessels of interest | 3-14 ml for right or left coronary artery | 45 ml (10-80 ml) | |
| Maximum dose | 225 ml | 225 ml | 225 ml | 225 ml |
| Ioversol (Optiray) (320 mgI/ml) | 2-12 ml | 40 ml (30-50 ml) | 45 ml (10-80 ml) | |
| Maximum dose | 200 ml | |
| Iobitridol (Xenetix) (350 mgI/ml) | 10-80 ml | 30-60 ml | |
| Maximum dose | 250 ml | |
| Iodixanol (Visipaque) (320 mgI/ml) | Adult doses suggestion | | | Carotid arteries: 10-14 ml | Vertebal arteries: 10-12 ml | Right coronary artery: 3-8 ml | Left coronary artery: 5-10 ml | Left ventricle: 20-45 ml | Renal arteries: 8-18 ml | Aortography: 30-70 ml | Major aorta branch: 10-70 ml | Peripheral arterries: 15-30 ml | Aortofermoral runoff: 20-90 ml | |
| Maximum dose | 250 ml (80 gI) | 175 ml (80 gI) | | | | | | | | | | |
Table 4 – Suggested single injection of adult doses and maximum total dose for non-ionic contrast media by Intravenous injection [31].

| Non-ionic contrast media | Computerized axial tomography, Body | Computerized axial tomography of head (brain) | Intravenous pyelogram (urography) | Angiocardiography-Coronary Arteriography/ Ventriculography | Angiocardiography-ventriculography or nonselective opacification of multiple coronary arteries | Aortography | Arteriography, peripheral | Arteriography, selective visceral | Arteriography of cerebral arteries | Renal arteriography | Venography |
|-------------------------|------------------------------------|-----------------------------------------------|--------------------------------|-------------------------------------------------|-------------------------------------------------|------------|--------------------------------|--------------------------------|---------------------------------|---------------------------------|-----------------|----------------|
| Iopromide (Ultravist) (300 mgI/ml) | 50-200 ml for bolus IV injection | 100-200 ml for rapid IV infusion | 50-200 ml | 300 mgI/Kg | | | | | | | | |
| Maximum dose | 200 ml (60 gl) | 200 ml (60 gl) | 100 ml (30 gl) | | | | | | | | | |
| Iopromide (Ultravist) (370 mgI/ml) | 41-162 ml for bolus IV injection | 81-162 ml for rapid IV infusion | 41-162 ml | | | | | | | | | |
| Maximum dose | 162 ml (60 gl) | 162 ml (60 gl) | | 5-40 ml for femoral or subclavian | 25-50 ml for aorta for a distal runoff | | | | | | |
| Iopamidol (Iomartsol) (300 mgI/ml) | 100-200 ml | 100-200 ml | 2-0-2.5 ml/Kg | 50 ml | | | | | | | | |
| Maximum dose | 200 ml (60 gl) | 200 ml (60 gl) | | | | | | | | | | |
| Iopamidol (Iomartsol) (370 mgI/ml) | 81-162 ml | 81-162 ml | | | | | | | | | | |
| Maximum dose | 200 ml (60 gl) | 200 ml (60 gl) | | | | | | | | | | |
| Omnipaque (Iohexol) (300 mgI/ml) | 50-200 ml | 75-150 ml | 200-350 ml/Kg | 30-90 ml | | | | | | | | |
| Maximum dose | 291 ml | | | | | | | | | | | |
| Omnipaque (Iohexol) (350 mgI/ml) | 60-100 ml | 350 ml | 200-350 ml/Kg | 5 ml (3-14 ml) | 40 ml (30-60 ml) | 20-70 ml | | | | | | |
| Maximum dose | | | | | | | | | | | | |
| Ioversol (Optiray) (320 mgI/ml) | 25-75 ml (bolus injection) | 50-150 ml | 50-75 ml | 8 ml (2-10 ml) for the left coronary; 6 ml (1-10 ml) for the right coronary artery | | | | | | | | |
| Maximum dose | 150 ml | 250 ml | | | | | | | | | | |
| Ioversol (Optiray) (350 mgI/ml) | 25-75 ml (bolus injection) | 50-75 ml | | | | | | | | | | |
| Maximum dose | 150 ml | 250 ml | 50-100 ml | | | | | | | | | |
| Iobitridol ( Xenetix) (300 mgI/ml) | | | | | | | | | | | | |
| Maximum dose | | | | | | | | | | | | |
| Iobitridol (Xenetix) (350 mgI/ml) | | | | | | | | | | | | |
| Maximum dose | 1-1-5 ml/Kg | 155-330 ml | 30-60 ml (3-5 ml/Kg) | 10-80 ml | 105-205 ml | | | | | | |
| Maximum dose | 1-1-5 ml/Kg | | | | | | | | | | | |
| Iodixanol (Visipaque) (320 mgI/ml) | 75-150 ml | 75-150 ml | 1 ml/Kg | 20 ml | | | | | | | | |
| Maximum dose | 150 ml (80 gl) | 150 ml (80 gl) | 100 ml (80 gl) | | | | | | | | | | |
Table 5 – Suggested single injection of adult doses and maximum total dose for non-ionic contrast media by Intrathecal route injection [31].

| Non-ionic contrast media          | Myelogram - cervical myelogram (via lumbar injection) | Myelogram - total columnar myelography | Myelogram - thoracic | Myelogram - spinal cord |
|-----------------------------------|-------------------------------------------------------|----------------------------------------|----------------------|------------------------|
| Iopamiro (Iopamidol) (300 mgI/ml) | Adult doses suggestion: 10 ml                           | 10 ml                                  |                      |                        |
|                                   | Maximum total dose:                                      |                                        |                      |                        |
| Iohexol (Omnipaque) (300 mgI/ml)  | Adult doses suggestion: 4-10 ml                          | 6-10 ml                                | 6-10 ml              |                        |
|                                   | Maximum total dose: 3060 mgI                             | 3060 mgI                               | 3060 mgI             |                        |

Fig. 3 - Advanced Cardiovascular Life Support (ACLS) guideline for the management and treatment of adverse effects on anaphylactic reaction.

Acknowledgments

This work was supported by the grant from China Medical University Hospital, Taichung, Taiwan (DMR-107-123). The authors also would like to express our gratitude to Miss Huei-Min Chen for drug information supports.

REFERENCES

[1] La Grutta L, Toia P, Maffei E, Cademartiri F, Lagalla R, Midiri M. Infarct characterization using CT. Cardiovasc Diagn Ther. 2017; 7: 171-88.
Fig. 4 - Management and treatment of anaphylactic reaction by iodinated CM is proposed in 2017 RSROC Contrast Media Manual.

Fig. 5 - Three factors are responsible for contrast-induced nephropathy.

[2] Rybicki FJ, Piazzo K, Prior R, Wake N, Dill KE. Iodinated contrast injection data from a new technology. Radiol Technol. 2012; 84: 120-5.

[3] Meunier B, Joskin J, Damas F, Meunier P. Iodinated contrast media and iodine allergy: myth or reality? Rev Med Liege. 2013; 68: 465-9.

[4] Goodwill PW, Saritas EU, Croft LR, Kim TN, Krishnan KM, Schaffer DV, et al. X-space MPI: magnetic nanoparticles for safe medical imaging. Adv Mater. 2012; 24: 3870-7.

[5] Harbron RW, Ainsbury EA, Bouffler SD, Tanner RJ, Eakins JS, Pearce MS. Enhanced radiation dose and DNA damage associated with iodinated contrast media in diagnostic x-ray imaging. Br J Radiol. 201720170028.

[6] Mamoulakis C, Tsarouhas K, Fragkiadoulaki I, Heretis I, Wilks MF, Spandidos DA, et al. Contrast-induced nephropathy: Basic concepts, pathophysiological implications and prevention strategies. Pharmacol Ther. 2017.

[7] Prezzi D, Khan A, Goh V. Perfusion CT imaging of treatment response in oncology. Eur J Radiol. 2015; 84: 2380-5.

[8] Price DB, Ortiz AO. Myelography: From Lipid-Based to Gado-linum-Based Contrast Agents. Magn Reson Imaging Clin N Am. 2017; 25: 713-24.

[9] Cheng KT. Lipiodol-loaded poly(oxyethylene)-block-poly(oxypropylene)-block-poly(oxyethylene) triblock copolymers/polyethylene glycol-nanoparticles. In. Molecular Imaging and Contrast Agent Database (MICAD). ed. Bethesda (MD): 2004.

[10] Cheng KT. Ioxilan carbonate particles. In. Molecular Imaging and Contrast Agent Database (MICAD). ed. Bethesda (MD): 2004.

[11] Lee SY, Rhee CM, Leung AM, Braverman LE, Brent GA, Pearce EN. A review: Radiographic iodinated contrast media-induced thy-
Fig. 6 - The detailed molecular mechanisms of contrast-induced nephropathy.

Contrast media

- Renal vasoconstriction
- ↑ Tubular Flow
- ↑ Tubular pressure
- ↑ O2 consumption
- ↑ Tubular intracellular Ca++
- ↑ Reactive oxygen species (ROS)
- ↑ Tubular fluid Viscosity
- ↑ Tubular reabsorption
- Medullary hypoxia
- Changes in Erythrocyte membrane skeleton
- Vasa Recta constriction
- Tubular obstruction
- Tubular cell damage
- Autophagic and Apoptotic cell death
- ↓ Glomerular filtration rate (GFR)
- ↓ Renal blood flow (RBF)
- Tubular fluid viscosity
- Tubular pressure
- Tubular reabsorption
- Tubular intracellular Ca++
- Tubular cell damage
- Autophagic and Apoptotic cell death
- ↓ Glomerular filtration rate (GFR)
- ↓ Renal blood flow (RBF)

Contrast-induced nephropathy (CIN)

Adverse reactions, prevention and treatment. Harefuah. 1995; 128: 719-23.

Singh J, Daftary A. Iodinated contrast media and their adverse reactions. J Nucl Med Technol. 2008; 36: 69-74; quiz 76-7.

Weisbord SD, Palevsky PM. Iodinated contrast media and the role of renal replacement therapy. Adv Chronic Kidney Dis. 2011; 18: 199-206.

Weisbord SD. Iodinated contrast media and the kidney. Rev Cardiovasc Med. 2008; 9 Suppl 1: S14-23.

Pintassilgo Santos A, Mascarenhas Gaivao A, Tavares A, Ferreira S. Iodinated contrast agents. Acta Med Port. 2009; 32: 315-26.

Erley C. Iodinated contrast agent-induced nephropathy. Radiol. 2007; 47: 761-7.

https://www.micromedexsolutions.com/home/dispatch/ssl/true. Published 2017. Updated Accessed.

Hu XH, Gong XY, Hu P. Transient small bowel angioedema due to intravenous iodinated contrast media. World J Gastroenterol. 2012; 18: 999-1002.

2017 RSROC Contrast Media Manual (https://www.rsroc.org.tw/DB/Info/file/123-1.pdf). Updated Published. Updated Accessed.

Thomsen HS, Morcos SK. Radiographic contrast media. BJU Int 2000; 86 Suppl 1:1-10.

Almen T. The etiology of contrast medium reactions. Invest Radiol. 1994; 29 Suppl 1: S37-45.

Beckert K.R, MAK, Langer J.M. Safe Use of Contrast Media: What the Radiologist Needs to Know. Radiographics. 2015; 35: 1738-50.

Modi K, Dulebohn SC. Contrast Induced Nephropathy. In. StatPearls. ed. Treasure Island (FL): StatPearls. ed. Treasure Island (FL): 2017.

Ursatia AA, Kharkov EI, Petrova MM, Urista OV, Kotikov AR, Kiselev AN. Contrast induced nephropathy in the older age group patients. Adv Gerontol. 2017; 30: 306-10.

Wong GT, Lee EY, Irwin MG. Contrast induced nephropathy in vas-

roid dysfunction. J Clin Endocrinol Metab. 2013; 100: 376-83.

Costa N. Understanding contrast media. J Infus Nurs. 2004; 27; 302-12.

Bettmann MA, Morris TW. Recent advances in contrast agents. Radiol Clin North Am. 1986; 2: 347-57.

Spampinato MV, Abid A, Matheus MG. Current Radiographic Iodinated Contrast Agents. Magn Reson Imaging Clin N Am. 2017; 25: 697-704.

Schrader R. Contrast material-induced renal failure: an overview. J Interv Cardiol. 2005; 18: 417-23.

Pugh ND, Griffith TM, Karlsson JO. Effects of iodinated contrast media on peripheral blood flow. Acta Radiol Suppl. 1995; 399: 155-63.

Stolberg HO, McClenman BL. Ionic versus nonionic contrast use. Curr Prob Diagn Radiol. 1991; 20: 47-88.

ten Dam MA, Wetzels JF. Toxicity of contrast media: an update. Neth J Med. 2008; 66: 416-22.

Campbell KL, Hud LM, Adams S, Andrel J, Ballas SK, Feldman AM, et al. Safety of iodinated intravenous contrast medium administration in sickle cell disease. Am J Med. 2012; 125: 100 e11-6.

Katzberg RW, Barrett BJ. Risk of iodinated contrast material-induced nephropathy with intravenous administration. Radiology. 2007; 243: 622-8.

Runge VM. A review of contrast media research in 1999-2000. Invest Radiol. 2001; 36: 123-30.

McCullough PA. Renal safety of iodixanol. Expert Rev Cardiovasc Ther. 2006; 4: 655-61.

Mrk B. Renal Safety of Iodinated Contrast Media Depending on Their Osmolarity - Current Outlooks. Pol J Radiol. 2016; 81: 157-65.

Dawson P. The non-ionic isotonic contrast agents. Perspectives and controversies. Eur Radiol. 1996; 6 Suppl 2: S20-4.

Konen E, Apter S, Morag B, Izhchak Y. Iodinated contrast media: adverse reactions, prevention and treatment. Harefuah. 1995; 128: 719-23.

Singh J, Daftary A. Iodinated contrast media and their adverse reactions. J Nucl Med Technol. 2008; 36: 69-74; quiz 76-7.

Weisbord SD, Palevsky PM. Iodinated contrast media and the role of renal replacement therapy. Adv Chronic Kidney Dis. 2011; 18: 199-206.

Weisbord SD. Iodinated contrast media and the kidney. Rev Cardiovasc Med. 2008; 9 Suppl 1: S14-23.

Pintassilgo Santos A, Mascarenhas Gaivao A, Tavares A, Ferreira S. Iodinated contrast agents. Acta Med Port. 2009; 32: 315-26.

Erley C. Iodinated contrast agent-induced nephropathy. Radiol. 2007; 47: 761-7.

https://www.micromedexsolutions.com/home/dispatch/ssl/true. Published 2017. Updated Accessed.

Hu XH, Gong XY, Hu P. Transient small bowel angioedema due to intravenous iodinated contrast media. World J Gastroenterol. 2012; 18: 999-1002.

2017 RSROC Contrast Media Manual (https://www.rsroc.org.tw/DB/Info/file/123-1.pdf). https://www.rsroc.org.tw/DB/Info/file/123-1. Published 2017. Updated Accessed.

Thomsen HS, Morcos SK. Radiographic contrast media. BJU Int 2000; 86 Suppl 1:1-10.

Almen T. The etiology of contrast medium reactions. Invest Radiol. 1994; 29 Suppl 1: S37-45.

Beckert K.R, MAK, Langer J.M. Safe Use of Contrast Media: What the Radiologist Needs to Know. Radiographics. 2015; 35: 1738-50.

Modi K, Dulebohn SC. Contrast Induced Nephropathy. In. StatPearls. ed. Treasure Island (FL): 2017.

Ursatia AA, Kharkov EI, Petrova MM, Urista OV, Kotikov AR, Kiselev AN. Contrast induced nephropathy in the older age group patients. Adv Gerontol. 2017; 30: 306-10.

Wong GT, Lee EY, Irwin MG. Contrast induced nephropathy in vas-
**Table 6 − In vitro studies of mechanisms on contrast-induced nephropathy (CIN) in iodinated contrast media.**

| In-vitro cell lines | Iodinated contrast media | Dose | Time of treatment | Results | References |
|---------------------|--------------------------|------|-------------------|---------|------------|
| KRK52-E (Rat kidney epithelial cell) | Iodixanol (Visipaque) | 150 mgI/ml | 0.5 h, 1h, 3 h, 6 h, 12 h, 24 h | 1. Decreasing cell proliferation by MTT assay. 2. Induce cells death by Trypan blue assay. 3. Increasing apoptosis by hematoxylin-stained. | [60] |
| | Ioversol (Optiray) | | | | |
| | Iohexol (Omnipaque) | | | | |
| | Iopromide (Ultravist) | | | | |
| | NRK52-E (Rat tubular cells) | Iohexol (Omnipaque) | 100 mgI/ml | 24 h | 1. Decreasing cell proliferation by MTT assay. 2. Increasing apoptotic cells by TUNEL assay. 3. Increasing caspase-3, caspase-9 and cytochrome c protein levels by western. 4. Decreasing cell viability by iohexol was aggravated with 3-MA pretreatment. | [61] |
| | LLC-PK1 (Pig renal tubular epithelial cells) | Iohexol (Omnipaque) | 100 mgI/ml | 24 h | 1. Decreasing cell proliferation by MTT assay. 2. Increasing apoptotic cells by TUNEL assay. 3. Increasing caspase-8, caspase-9 and caspase-3 protein levels by western. | [62] |
| | | Iodixanol (Visipaque) | | | | |
| | HK-2 (human embryonic proximal tubule) | Iopamiro (Iopamidol) | 200 mgI/ml | 0 h, 12 h, 24 h | 1. Decreasing cell proliferation by MTT assay. 2. Increasing apoptotic cells by TUNEL assay. 3. The mRNA level of Bax was increased and Bcl-2 was decreased by qPCR. 4. Increasing Bax, caspase-3 protein levels and decreasing Bcl-2, HSP70 protein levels by western. | [63] |
| | LLC-PK1 (Pig renal tubular epithelial cells) | Iodixanol (Visipaque) | 4.7-75 mgI/ml | 2h, 24h | 1. Decreasing cell proliferation by MTT assay. | [58] |
| | HK-2 (human embryonic proximal tubule) | Iopromide (Ultravist) | 40 mgI/ml | 24-72 h | 1. Caused the breaking of intercellular connections and cell migration by scratch assay. 2. Increasing SGK, SNAIL1, CTGE, COL1A1 mRNA levels by qPCR | [64] |
| | | 20 mgI/ml | | | | |
| | | 10 mgI/ml | | | | |
| | LLC-PK1 (Pig renal tubular epithelial cells) | Ioversol (Optiray) | 100 mgI/ml | 24 h | 1. Increasing caspase-3 protein activity by caspase-3 activity assay | [56] |
| | HK-2 (human embryonic proximal tubule) | Ioversol (Optiray) | 100 μL/ml | 24 h | 1. Decreasing cell proliferation by MTT and LDH assay. | [55] |
| | | 200 μL/ml | | | | |
| | HK-2 (human embryonic proximal tubule) | Iodixanol (Visipaque) | 25 mgI/ml | 2h, 4h, 8h, 24h | 1. Decreasing cell proliferation by CellTiter 96 assay. | [53] |
| | | 50 mgI/ml | | | | |
| | | 100 mgI/ml | | | | |
| | | 200 mgI/ml | | | | |
| | LLC-PK1 (Pig renal tubular epithelial cells) | Iodixanol (Visipaque) | 18.75-75 mgI/ml | 24 h | 1. Decreasing cell proliferation by BrdU assay 2. Increasing apoptotic cells by cytoplasmic oligonucleosomes ELISA assay. | [52] |

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[40] Davenport MS, Cohan RH, Ellis JH. Contrast media controversies in 2015: imaging patients with renal impairment or risk of contrast reaction. AJR Am J Roentgenol. 2015; 204: 1174-81.

[41] Homma K. Contrast-induced Acute Kidney Injury. Keio J Med. 2016; 65: 67-73.

[42] McCullough PA, Choi JP, Feghali GA, Schussler JM, Stoler RM, Vallabah RC, et al. Contrast-Induced Acute Kidney Injury. J Am Coll Cardiol. 2016; 68: 1465-73.

[43] Genovesi E, Romanello M, De Caterina R. Contrast-induced acute kidney injury in cardiology. G Ital Cardiol (Rome) 2016; 17: 984-1000.

[44] Ozkok S, Ozkok A. Contrast-induced acute kidney injury: A review of practical points. World J Nephrol. 2017; 6: 86-99.

[45] Chalikias G, Drosos I, Tziakas DN. Contrast-Induced Acute Kidney Injury: An Update. Cardiovasc Drugs Ther. 2016; 30: 215-28.

[46] Mohammed NM, Maftouz A, Achkar K, Rafie IM, Hajar R. Contrast-induced Nephropathy. Heart Views. 2013; 14: 106-16.
Wichmann JL, Katzberg RW, Litwin SE, Zwerner PL, De Cecco CN, Vogl TJ, et al. Contrast-Induced Nephropathy. Circulation. 2015; 132: 1931-6.

Contrast-Induced Nephropathy (CIN): Current State of the Evidence on Contrast Media and Prevention of CIN. In. Comparative Effectiveness Review Summary Guides for Clinicians. ed. Rockville (MD): 2007.

Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP. Contrast-Induced Nephropathy: An "All or None" Phenomenon? Angiology. 2015; 66: 508-13.

Lameire NH. Contrast-induced nephropathy--prevention and risk reduction. Nephrol Dial Transplant. 2006; 21: i11-23.

Bagshaw SM, Culleton BF. Contrast-induced nephropathy: epidemiology and prevention. Minerva Cardioangiol. 2006; 54: 109-29.

Heinrich MC, Scheer M, Heckmann M, Kuefner MA, Uder M. Iodixanol induces apoptotic and antiproliferative effects but no necrotic cell death in renal proximal tubular cells in vitro. Rofo 2009; 181: 349-54.

Yao L, Kolluru GK, Kevil CG, Zhang WW. Intravascular radiocontrast iodixanol increases permeability of proximal tubule epithelium: a possible mechanism of contrast-induced nephropathy. Vase Endovascular Surg. 2013; 47: 632-8.

Lerch M, Keller M, Britschgi M, Kanny G, Tache V, Schmid DA, et al. Cross-reactivity patterns of T cells specific for iodinated contrast media. J Allergy Clin Immunol. 2007; 119: 1529-36.

Zager RA, Johnson AC, Hanson SY. Radiographic contrast media-induced tubular injury: evaluation of oxidant stress and plasma membrane integrity. Kidney Int. 2003; 64: 128-39.

Yokomaku Y, Sugimoto T, Kume S, Araki S, Isshiki K, Chin-Kanasaki M, et al. Asialoerythropoietin prevents contrast-induced nephropathy. J Am Soc Nephrol. 2008; 19: 321-8.

Duan S, Zhou X, Liu F, Peng Y, Chen Y, Pei Y, et al. Comparative cytotoxicity of high-osmolar and low-osmolar contrast media on HKCs in vitro. J Nephrol. 2006; 19: 717-24.

Heinrich M, Scheer M, Heckmann M, Bautz W, Uder M. Reversibility and time-dependency of contrast medium induced inhibition of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) conversion in renal proximal tubular cells in vitro: comparison of a monomeric and a dimeric nonionic iodinated contrast medium. Invest Radiol. 2007; 42: 732-8.

Yang JS, Lu CC, Kuo SC, Hsu YM, Tsai SC, Chen SY, et al. Autophagy and its link to type II diabetes mellitus. Biomedicine. (Taipei) 2017; 7: 8.

Jensen H, Doughty RW, Grant D, Myhre O. The effects of the iodinated X-ray contrast media iodixanol, iohexol, iopromide, and ioversol on the rat kidney epithelial cell line NRK 52-E. Ren Fail. 2011; 33: 426-33.

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.

Kolyada AY, Liangos O, Madias NE, Jaber BL. Protective effect of erythropoietin against radiocontrast-induced renal tubular epithelial cell injury. Am J Nephrol. 2008; 28: 203-9.

He X, Yang J, Li L, Tan H, Wu Y, Rui P, et al. Atorvastatin protects against contrast-induced nephropathy via anti-apoptosis by the up-regulation of Hsp27 in vivo and in vitro. Mol Med Rep. 2017; 15: 1963-72.

Sayarlioglu H, Okuyucu A, Bedir A, Salis O, Yenen E, Bekfilavioglu G, et al. Is there any role of epithelial to mesenchymal transition in the pathogenesis of contrast nephropathy? Ren Fail. 2016; 38: 1249-55.