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Contrast-related acute kidney injury and its prevalence among the elderly – a systematic review

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Summary

Acute kidney injury (AKI) is a disease associated with deterioration of renal function resulting in accumulation of detrimental metabolic products and decreased diuresis. With age, numerous anatomical and physiological changes are observed that impair renal function, which is particularly expressed among the elderly. The first reports of contrast-induced AKI (CIN) were reported in a paper by Bartels et.al, which described cases of AKI in patients following pyelography with intravenous contrast administration. Currently, despite numerous studies exploring the issue, the role of contrast media (CM) as the main factor responsible for the development of CIN is disputed, and the effect of CM on the development of AKI appears to be purely coincidental. However, in the absence of conclusive evidence ruling out or confirming this relationship, another diagnostic method should be considered before administering CM, especially in high-risk patients, or low osmolality, low-volume agents should be used if necessary. *Geriatria 2022;16:195-205. doi: 10.53139/G.20221628*

Keywords: contrast induced nephropathy; contrast induced acute kidney injury; prevention of contrast induced nephropathy

Introduction

Acute kidney injury (AKI) is a disorder associated with deterioration of renal function resulting in accumulation of detrimental metabolic products and decreased diuresis. With age, numerous anatomical and functional changes that impair renal function are observed [1]. Prominent among the numerous abnormalities are a reduction in the number of glomeruli and progressive sclerosis of the remaining glomeruli, thickening of the basement membrane in the renal vessels and progressive fibrosis of the interstitium (table I). Progressive alterations with age contribute to an increased risk of developing AKI, which is particularly expressed in the elderly [2]. There are 3 distinct forms of AKI – pre-renal, renal and post-renal [3]. Among the causes of AKI are hypovolemia, adverse effects of drugs, glomerulonephritis, or administration of a contrast agent (table II). According to Kidney Disease: Improve Global Outcome (KDIGO), AKI induced by contrast agent administration is found by an increase in creatinine concentration by 25% or by ≥0.5 mg/dl within 72h of contrast agent administration [4]. The first reports of contrast-induced AKI (CIN) were reported in the work of Bartels et.al, who described cases of AKI in patients after pyelography with intravenous contrast administration [5]. Despite the lack of conclusive evidence in the Bartels et.al. study linking AKI to contrast medium (CM) administration, the concept of CIN became widespread and is still upheld today. This has led to numerous developments, both with regard to the CM used in diagnostic imaging and attempts to prevent the development of CIN. Nowadays, despite numerous studies exploring this topic, the role of CM as the main factor responsible for the development of AKI after imaging diagnosis using CM is questioned and it is emphasized that the influence of CM on the development of AKI may be coincidental. This leads to a situation in which diagnostic procedures using CM are sometimes delayed until the results improve, which in elderly patients, in whom renal function parameters are often deteriorated, may affect their prognosis. This article summarizes recent reports regarding the role of CM in the development of AKI among elderly .

Methodology

In preparing our article, we searched the PubMed database for literature items from 1950 to 2022. To search for papers, we used keywords such as contrast induced nephropathy, contrast induced acute kidney injury, prevention of contrast induced nephropathy

Table I. Anatomical and physiological changes observed in the elderly

Anatomical changes	Physiological changes
Reduction in the size and weight of the kidneys	Reduction in renal vascular flow with age (by 30 – 50%) with a tendency to increase ischemic changes in the kidneys
Fibroblastic hyperplasia in archuate arteries and arterioles in kidneys	Decrease in glomerular filtration rate with age (by 30 – 50%) with a tendency toward impaired renal excretory function
Focal thickening of the basement membrane in renal vessels	Decrease in the ability to thicken and dilute urine with a tendency toward dehydration or congestion
Reduction in the total number of glomeruli (by 30 – 50%) with progressive sclerosis of the remaining glomeruli	Decrease in Na+ conservation capacity with tendency to hyponatremia and orthostatic hypotension
Gradual fibrosis with minor inflammatory reaction of the renal interstitium	Decrease in total K+ pool and its exchangeable function with a tendency towards hypo- and hyperkalemia
Shortening the length and capacity of renal tubules	Decrease in the activity of the renin- angiotensin-aldosterone system with a tendency toward hypo- and hyperkalemia
Focal thickening of the basement membrane of the renal tubules	Decrease in urine acidification capacity independent of decrease in glomerular filtration rate with tendency to develop tubular acidosis

Table II. The most common causes of AKI development

Pre-renal causes	Renal causes	Post-renal causes
Hypovolemia	Glomerular and small vessel diseases	Disruption of urinary outflow through the ureters
Decreased cardiac output	Acute renal injury caused by endo- or exogenous toxins, or in cases of prolonged pre-renal AKI	Disruption of urinary outflow from the bladder
Nephrotoxic drugs	Tubulo-interstitial nephritis	Disruption of urinary outflow at the level of the urethra
Obstruction or impairment of renal vascular tone	Acute rejection of transplanted kidney	
	Presence of crystals inside the tubules	

combined with the phrase in elderly patients. Mainly review papers, original papers and case reports were found. The final list of literature was selected on the basis of subjective evaluation of applicability to the topic of the paper.

Patophysiology of CIN

CIN is a complication arising from a variety of pathomechanisms. Among the suspected causes of CIN development are direct nephrotoxic effects of CM, hemodynamic changes, oxidative stress, apoptosis and local inflammation.

Direct nephrotoxic effects of CM

CMs used in diagnostic procedures are divided according to the ratio of CM osmolality to plasma osmolality into isoosmolal or hypoosmolal [6]. High-osmolality contrast agents (HOCM) are not used in practice due to their cytotoxic properties [7]. CMs acting on both renal tubular epithelial cells and vascular epithelial cells can lead to their swelling, apoptosis and ultimately necrosis, however the exact pathomechanism of these changes is still unknown [8]. It is suspected that when CM is administered, it enters the renal vasculature, where it leads to a brief contraction of the vascular musculature and thus a transient reduction in renal blood flow [8]. The decrease in flow

can lead to the accumulation of contrast agent in the epithelial cells of the renal tubules and consequently cause or exacerbate their damage and inflammation through high osmolality or direct action of iodine on these cells [9]. In damaged cells, oxygen free radicals are generated, which can induce through a number of signaling pathways apoptosis in neighboring cells and ultimately lead to their necrosis [10]. Necrotic altered renal tubule epithelial cells become detached from the basement membrane entering the lumen of the renal tubules leading to their obstruction and consequent deterioration of renal function [10]. Moreover, Romano et al. in their work showed that CMs induce apoptosis of renal tubular epithelial cells, the effect of which is both dose- and time-dependent [9]. This effect is based on the activation of caspases that induce apoptosis in these cells.

Hemodynamic changes

The intravascular supply of CMs most likely affects the renal vasculature through a series of consecutive processes. Initially, transient vasodilatation occurs, followed by vasoconstriction with increased vascular resistance and decreased renal vascular blood flow [11]. At first, renal vascular endothelial cells present an effective response to vasoconstriction in the form of increased production of prostaglandins and nitric oxide to increase oxygen delivery to cells and improve blood flow in the renal vessels [11]. However, after a certain period of time, the mechanisms counteracting vasoconstriction are exhausted, leading to renal ischemia and a decrease in glomerular filtration rate (GFR) [11]. Moreover, this effect is enhanced in the renal medulla due to the characteristic anatomy of the renal vasculature, which under physiological conditions restricts blood supply to certain elements of the loop of Henle. This effect is exacerbated by exposure of endothelial cells to CMs [12]. In the elderly, this effect may be further exacerbated by the physiological reduction in blood flow associated with aging [1].

Osmolality of the contrast agents

The type of CMs used has effects on both blood in the blood vessels and fluid in the renal tubules. In the case of blood, CMs can increase the viscosity and osmolality of blood, which increases the risk of microembolic AKI [13]. In contrast, in the case of urine in the renal tubules, its viscosity increases exponentially as the concentration of contrast agents increases, slowing down the fluid in the renal tubules and thus prolonging the exposure of the epithelial cells of these tubules to contrast agents, which can lead to tubular damage and impaired renal function [14].

Oxidative stress and apoptosis

Intravenous CMs can affect the development of oxidative stress in two ways. First, these agents, by causing a direct cytotoxic effect on renal tubule epithelial cells, may contribute to mitochondrial damage, resulting in the release of cytochrome c and catalytic iron from the cells [8, 15]. The released cytochrome c is one of the factors that activate the mechanism of apoptosis, while free iron can enter into Haber-Weiss and Fenton reactions, resulting in the formation of free oxygen radicals (ROS), which consequently also leads to apoptosis of renal tubular epithelial cells [12, 16]. The second cause is the hypoxia accompanying reduced blood flow, as a result of which the availability of the primary substrate of oxidative phosphorylation, oxygen, is reduced [17]. This leads to a decrease in ATP synthesis and subsequent formation of oxygen free radicals. The oxygen free radicals formed in these pathways activate a number of kinases and signaling pathways that lead to apoptosis of renal tubular epithelial cells [17].

Inflammation

Another potential cause of the development of CIN could be the inflammation developed as a result of the administration of CMs. Zu et al. and Wang et al. in their studies showed that the administration of CMs led to an increase in inflammatory parameters such as c-reactive protein, IL-6, and TNF-a, as well as an increase in creatinine levels among the animals studies [18,19]. Meanwhile, the use of antithrombin III or renalase in these animals led to a reduction in the ongoing inflammation [18]. A proposed reason for the development of inflammation is the activation of NF-κB, which activates NLRP3, which in turn activates caspase 1, which changes pro-IL-1β into IL-1β [20]. Moreover, Kwasa et al. conducted a study involving 423 patients who had no risk factors for developing CIN and underwent CT scans with a contrast agent [21]. In 215 of the study group, c-reactive protein levels were elevated before the scan, while in 208, the levels were within normal limits. The results showed that those with elevated c-reactive protein levels had a higher relative risk of developing CIN [21]. It is important to remember that with age, the risk of autoimmunity

increases, and generalized inflammation with concomitant immune deficits is observed. This increases susceptibility to infectious diseases, which may further exacerbate the contribution of this component to the development of CIN [22].

Potential risk factors of CIN

Despite numerous studies analyzing the CIN phenomenon, there is a lack of conclusive evidence in the publicly available literature regarding the association of contrast agent use with AKI. However, these studies have made it possible to raise suspicions about groups of patients who may have a higher risk of CIN. These groups include patients with impaired renal function prior to contrast administration, with reduced renal perfusion, and patients who underwent imaging with high-osmolar contrast agents (table III).

Impaired renal function preceding contrast agent administration

Rudnick et al. conducted a study involving 1196 patients who were to undergo coronary angiography with either a nonionic contrast agent, iohexol, or an ionic contrast agent, sodium meglumine/diatrosate [23]. Patients were divided into four groups according to the presence of renal impairment and diabetes, and creatinine levels were measured before and after contrast administration. After coronary angiography, features of AKI were observed in 42 patients in the group that received megulmin/sodium diatrosate and 19 patients who received iohexol. Differences in nephrotoxicity between the two groups were limited to patients with impaired renal function or impaired renal function along with diabetes [23]. This may suggest that renal impairment alone diagnosed before CM administration or with concomitant diabetes mellitus increases the risk of developing AKI after administration of CMs. In contrast, Parfrey et al. studying patients with previously diagnosed renal impairment, diabetes mellitus, or both, did not find similar results [24]. The study included 488 patients, who were divided according to the presence or absence of the aforementioned comorbidities, followed by diagnostic imaging with contrast agents. After they were performed, clinically significant acute renal failure, diagnosed by the authors on the basis of an increase in creatinine > 50% from baseline values, was not found in either the group of patients with previously diagnosed renal impairment and diabetes or the group with normal renal function and diabetes. However, AKI, as determined by the authors on the basis of an increase in creatinine levels > 25% from baseline values, was diagnosed in 11.8% of patients with renal impairment diagnosed before the study, with or without concomitant diabetes. After excluding from this pool control subjects and those in whom the cause of AKI may have been unrelated to contrast agent administration, a result of 5.5% on the scale of the aforementioned patient group was obtained [24]. This may suggest that the coexistence of diabetes does not increase the risk of developing CIN regardless of baseline GFR.

However, inaccuracies regarding the diagnosis of AKI associated with CM supply should be noted. The lack of uniformity in the criteria for diagnosing CIN in the aforementioned papers makes it difficult to link CM use to AKI. Rudnick et al. diagnosed CIN by an increase in creatinine ≥ 1 mg/dl 48-72h after contrast administration, while Parfrey et al. defined CIN by a 25% increase in creatinine after CM administration. In addition, these works did not consider other factors that may have influenced the increase in creatinine concentration after CM administration.

Table III. CIN risk factors

Risk factors related to the patient's condition	Risk factors associated with the procedure performed
Pre-exisiting renal function insufficiency	High osmolality of iodine agent
Diabetic nephropathy	Excessive use of iodine agent
Advanced age (> 70 years old)	Repeated exposure of contrast agent within 72 hours
Hypertension	Imaging techniques
Cognitive heart failure	Nephrotoxic drugs
Anemia	
Periprocedural hypoperfusion	

Currently, due to the lack of hard evidence, it is assumed that concomitant deterioration of renal function may increase the risk of AKI associated with the administration of CMs (CA-AKI) than lead to CIN [25-27] . According to KDIGO, the risk of developing CA-AKI increases with successive classes of chronic kidney disease [28].

Reduction of perfusion in the renal vessels

Reduced blood perfusion in the renal vessels can be developed in a numerous diseases, including ones with concomitant heart failure (HF), shock or the ingestion of drugs that affect renal hemodynamics. Reduced renal blood flow, in turn, can contribute to prolonged exposure to contrast agents and thus to a decrease in renal filtration capacity, already reduced as a result of concomitant diseases. Wang et al. conducted a study among 1,674 patients diagnosed with HF of any class, in which they analyzed the effect of HF-related reductions in renal blood perfusion in these patients undergoing coronary angiography or coronary angioplasty on the risk of developing CIN [29]. An increased risk of developing CIN has been observed in patients with any form of heart failure; however, there was no trend toward a higher risk of CIN in any class of HF [29]. This may suggest that factors that reduce renal perfusion may increase the risk of developing CIN, or may be solely a coincidental factor not affecting the development of CIN

The osmolality of contrast agent

CMs used for diagnostic imaging are divided into high and low osmolality agents [6]. HOCMs have osmolality ranging from about 5-8 times higher than plasma osmolality; however, due to the higher risk of developing AKI, they are no longer used [7]. Low osmolality agents, on the other hand, are divided into those with an osmolality about 3 times higher than plasma osmolality (LOCM) and isoosmotic agents (IOCM) [10]. Moore et al. in their study subjected 929 patients to diagnostic imaging using HOCM and LOCM [30]. The development of AKI was determined by an increase in creatinine concentration of 33% or > 0.4 mg/dL from baseline. This study observed only a small difference in favor of LOCM in the risk of developing AKI in patients with previously diagnosed renal impairment [30]. In contrast, a study by Rudnick et al. observed that patients with baseline elevated creatinine levels or laboratory signs of kidney damage and concomitant diabetes who received HOCM were about 3-fold more likely to develop AKI than patients who received LOCM [23]. Of the studies comparing the effects of LOCM and IOCM on the risk of developing CIN, the Nephrotoxicity in High-Risk Patients Study of IsoOsmolar and Low-Osmolar Non-Ionic Contrast Media Study (NEPHRIC) stands out, which included 129 patients with baseline creatinine levels between 1.3 and 3.5 mg/dl, diabetes mellitus and clinical indications for invasive catheter angiography [31]. The incidence of CIN, defined by an absolute increase in creatinine concentration of 0.5 mg/dl, was 3% in the iodixanol group and 26% in the iohexanol group. The peak increase in creatinine concentration measured on the third day after CM administration was also significantly lower in the iodixanol group – iodixanol: 0.13 mg/dL vs. iohexol: 0.55 mg/dL [31]. However, the exclusively intra-arterial use of CMs, the small group of patients and the specific CMs gave little generalizability to these results. In 2009, Heinrich et al. presented a meta-analysis including 25 randomized control trials from 1950 to 2007, combining data on 3,270 patients [32]. The CMs studied included several non-ionic LOCMs and IOCMs – iodixanol. In patients with pre-existing renal failure and diabetes, there was no reduction in the incidence of CIN associated with the use of IOCMs compared to LOCMs other than iohexol . Regardless of the route of administration or pre-existing renal failure, the use of IOCMs compared to LOCMs other than iohexol had a significant effect on the relative risk of CIN [32]. Moreover, a 2010 meta--analysis by From et al. including 36 randomized trials from 1966 to 2009 and a total of 7166 patients, found no statistically significant difference between iodixanol and other LOCMs [33]. This may suggest that the risk of developing AKI as a result of LOCMs or IOCMs is low at baseline and does not differ regardless of the type of CM used.

Methods of preventing CIN

The risk of AKI in a patient undergoing diagnostic imaging with CMs is hard to estimate; however, it largely depends on renal function. When renal function as determined by GFR is unknown and the patient requires diagnostic imaging with CMs, CIN prevention should be based on strategies such as appropriate use of contrast agents, adequate hydration and pharmacotherapy.

Adequate use of contrasting agents

One of the recommended methods of CIN prevention is to use CMs with the lowest possible osmolality for diagnosis and to use the lowest possible volume of CMs [10]. Any iodine CM can induce AKI; however, the nephrotoxicity of these agents varies and depends primarily on their osmolality [6]. Among the studies analyzing the difference in potential nephrotoxicity between LOCMs and IOCMs, the study by Azzalini et al. that included 2,648 patients undergoing percutaneous coronary angioplasty stands out [34]. CIN was diagnosed in only 300 of the total group, with no statistically significant difference between the type of contrast agent used [34].

Increasingly, the use of CMs devoid of nephrotoxic effects, such as carbon dioxide or gadolinium, is being suggested to enable diagnostic imaging in patients allergic to iodine contrast agents [35,36]. The use of CO2 in diagnostic imaging makes it possible to significantly reduce the volume of iodine contrast agents used without compromising imaging quality. Chao et al. conducted a retrospective study involving 100 patients who underwent endovascular repair of an abdominal aortic aneurysm using digital subtractive angiography, which was performed with CO2 [37]. This reduced the mean volume of contrast agent from 148 ml to 27 ml without compromising imaging quality, increasing the risk of developing AKI, or requiring dialysis after the procedure [37]. In addition, Stegemann et al. showed that angiography performed with CO2 and a reduced volume of iodinated contrast agent significantly reduced the incidence of CIN in peripheral vascular interventions [36]. However, the potential neurotoxicity of CO2 limits its use in arteriography in blood vessels located above the diaphragm, including coronary angiography. Another agent that has been considered as an alternative to iodine contrast agents is gadolinium; however, its use has been associated with induction of AKI in patients with concomitant diabetes or nephrogenic systemic fibrosis in patients with grade 4 and 5 chronic kidney disease [35].

An element of prophylaxis with unclear effects on the development of AKI is the volume of CM used. Diab et al. conducted a study involving 43 patients with type 2 diabetes and impaired renal function who underwent coronary angiography using a modified balloon catheter [38]. Modification of this catheter allowed the authors to aspirate excess contrast agent from the coronary sinus by about 33%, resulting in a reduction in the incidence of AKI in these patients from 36% to 5.5%; however, this significantly increased the duration of the procedure. Another method being considered to reduce the volume of contrast agent administered is the AVERT system. In their study, Mehran et al. observed that among 578 patients with impaired renal function (eGFR 20 to 60 ml/min/1.73 m2) and at least two additional CIN risk factors who underwent coronary angiography or PCI, the use of this system, despite a reduction in the volume of CM used, did not reduce the incidence of AKI [39]. At this point, it is also important to note inaccuracies regarding the effect of the volume of CM used in diagnostic imaging on the risk of developing AKI. It has been suggested that the risk of developing AKI is higher after coronary angiography than after computed tomography with CM (CECT) due to the fact that the volume of CM used during coronary angiography is larger than the volume of CM used in CECT [40]. However, when contrast dose is expressed as a ratio of grams of iodine to GFR (gI/GFR), an increase in nephrotoxicity is observed as this ratio increases [41]. The average CM dose during coronary angiography is about 0.7 – 1.0 gI/GFR, and during CT about 0.9 gI/GFR, suggesting that the risk of CIN after coronary angiography and after CECT may be similar [41].

Hydration of the patient prior to administration of contrasting agents

Despite the widespread belief that it is absolutely necessary to hydrate patients undergoing diagnostic imaging with CMs, there is currently a lack of conclusive evidence to support the need for such management in every patient undergoing diagnostic imaging. The current recommended management is to identify the presence of risk factors for the development of CIN, such as AKI or class 4 or 5 chronic kidney disease, who are not on dialysis, and to include prophylactic fluid therapy for patients in this group if they do not present with symptoms of hydration or are on dialysis [42]. The A MAstricht Contrast-Induced Nephropathy Guidelines Study (AMACING) by Nijssen et al. attempted to demonstrate the effectiveness of prophylactic fluid therapy administered prior to diagnostic imaging with CMs [43]. This study included 660 patients aged ≥ 18 years, with GFR > 30 ml/min, previously undialyzed and with indications for hydration, who were then randomly assigned to groups with and without fluid therapy. In this study, no difference in the incidence of

AKI was observed between patients who received fluid therapy before the diagnostic procedure and those who did not [43]. A study by Kooiman et al. that analyzed the risk of developing CIN in patients with pulmonary embolism undergoing pulmonary angiography did not observe statistically significant differences regardless of the use and type of CIN prophylaxis used [44]. It included 139 patients with mild to moderate chronic kidney disease (CKD) who were separated into a group in which no prophylaxis was used and a group in which a 250-ml intravenous bolus of sodium bicarbonate was administered. The incidence of CIN was similar in both groups. This may indicate that the use of prophylactic fluid therapy before diagnostic imaging with contrast agents does not reduce the risk of developing CIN.

Pharmacological treatment methods

Among pharmaceuticals with possible risk-reducing effects on the development of CIN, statins and vasodilators stand out. The Protective Effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome (PRATO-ACS) study by Leoncinci et al. analyzed the effect of high-dose rosuvastatin therapy on the risk of developing CIN in patients with acute coronary syndrome [45]. This study included 504 patients randomly assigned to rosuvastatin-treated and non-rosuvastatin-treated groups. It was observed that the incidence of CIN was significantly lower in the statin-taking group compared to the non-statin-taking group – 6.7% vs. 15.1% [45]. Similar results were obtained by Quintavalle et al. who studied the effect of atorvastatin use on the risk of developing CIN in patients with chronic renal failure [46]. This study included 410 patients who were randomly assigned to a group taking atorvastatin and not taking a statin. Both groups received high doses of N-acetylcysteine and sodium bicarbonate solution before diagnostic imaging with contrast agents. The results of this study showed that there was a reduced risk of developing CIN among patients receiving statins compared to those who did not receive statins – 4.5% vs. 17.8% [46]. The results of this study may suggest that statins may reduce the risk of developing CIN in patients with risk factors for this entity.

Common, albeit with an unproven effect, pharmaceuticals used for the prevention of CIN are antioxidants such as N-acetylcysteine, or sodium bicarbonate. One of the suspected pathomechanisms for the development of CIN is the formation of ROS, which through a series of changes such as lipid peroxidation, damage to intracellular proteins, and DNA damage. Weisbord et al. conducted a study that analyzed the effectiveness of sodium bicarbonate and N-acetylcysteine in preventing CIN in patients at high risk of developing this complication [47]. This study included 5177 patients who were randomly assigned to a group receiving sodium bicarbonate as prophylaxis or receiving N-acetylcysteine as prophylaxis. The results of this study showed that in the group receiving sodium bicarbonate prophylaxis, 4.4% of patients developed CIN, compared to 4.7% of patients receiving saline solution. In contrast, in the group receiving prophylactic N-acetylcysteine, the development of CIN was observed among 4.6% of patients compared to 4.5% of patients receiving placebo [47]. This may indicate that both sodium bicarbonate and N-acetylcysteine do not reduce the risk of developing CIN.

The last of the drug groups to be studied are vasodilators such as theophylline, 5-phosphodiesterase inhibitors and calcium channel blockers. The effect of theophylline, which is an inhibitor of receptors for adenosine responsible for vasoconstriction, on the risk of developing CIN was examined in a mentaanalysis by Dai et al. [48]. This study included 1,412 patients undergoing diagnostic imaging with CMs who received theophylline with or without N-acetylcysteine, or no theophylline but with or without N-acetylcysteine. The results of this study showed that a reduction in the risk of developing CIN was observed in the group receiving theophylline [48]. Iordache et al. conducted a study on rats in which sildenafil, tadalafil or N-acetylcysteine were used prior to contrast agent administration [49]. The diagnostic procedure was followed by histopathological examination of the kidneys of these animals, in which less severe inflammatory changes were observed compared to those observed in the kidneys of animals that had developed CIN [49]. This may suggest that sildenafil and tadalafil inhibiting the metabolism of cyclic guanosine monophosphate reduces the risk of CIN. The effect of calcium channel blockers on the development of CIN was studied by Yin et al [50]. It included 868 patients receiving amlodipine and 1,798 not receiving amlodipine before contrast administration. The results showed that the use of amlodipine before contrast exposure significantly reduced the incidence of CIN [50]. This may suggest that reducing

Ca2+ overload in renal tubule cells may reduce the risk of developing CIN.

Controversy surrounding CIN

CIN is a relatively new and incompletely understood phenomenon that requires further exploration for more profound understanding. In recent years, there has been an increasing number of papers casting doubt on the effect of CM use on the development of AKI. This is due to the publication of newer and newer studies, in which a similar risk of developing AKI is obtained regardless of the use of CMs. The risk of nephrotoxicity of the CMs used is a key element necessary to evaluate the appropriate diagnostic method, as this will allow the use of these agents only in patients who could benefit clinically.

The risk of developing CIN varies depending on the method of administration of contrasting agent

It has been suggested that intra-arterial administration of contrast agent is associated with a higher risk of CIN than intravenous delivery. Among the most recent studies analyzing this relationship, the study by Chaudhury et al. [51] stands out. They showed that patients who undergo diagnostic imaging with CM administered intravenously are more likely to have CIN than with intravenous administration of the contrast agent (16.5% vs. 12.5%) [51]. Gutierrez et al. investigating the differences between the concentration of contrast agent in blood flowing through the renal vasculature after its administration intra-arterially and intravenously, observed that a higher concentration of contrast agent is found in the renal vasculature after intra-arterial administration [52]. In contrast, van der Molen et al. observed that this situation occurs only when the contrast agent is administered above the exit of the renal arteries, and Nyman et al. suggested that there is no evidence to suggest a higher risk of developing CIN after intra-arterial administration of the contrast agent [41, 53]. The observed differences in nephrotoxicity between intravenous and intra-arterial administration of CM are most likely due to differences depending on the patient's condition, the presence of comorbidities, the type of procedure used, and the volume of contrast administered.

Lack of control group selection in studies analyzing CIN risk factors

One factor that may have contributed to the incorrect analysis of the relationship between CM use and the development of AKI was the study of potential risk factors for CIN without a control group. A number of observational studies have put forward the suspicion that CKD is supposed to be an independent risk factor for CIN, and that coexisting DM is a factor that increases the risk of developing CIN [54-57]. However, focusing attention solely on hospitalized patients may have led to incorrect conclusions about CIN risk factors, which may be dependent on other causes, and the use of CMs alone is coincidental

Misconceptions in drawing conclusions from clinical trials

Another factor that may have contributed to the suspicion that the observed increase in creatinine levels after CM administration is due solely to its administration. A retrospective study by Bruce et al. involving 11,588 patients compared the incidence of AKI in patients who underwent diagnostic imaging with and without CM administration [58]. The results of this study showed that the incidence of AKI in patients who received CM was similar to those who did not, suggesting that the use of CM cannot be considered the sole factor responsible for the development of CIN. Moreover, Aycock et al. conducted a meta-analysis including 28 papers, which showed that the use of CM compared to diagnostic imaging without CM showed no significant statistical difference regarding the incidence of AKI development [59]. In addition, Wilhelm-Leen et al. conducted an analysis of nearly 6 million hospitalizations to estimate the risk of developing AKI between patients who received CM and those who did not [60]. After adjusting the results for comorbidities, the risk of AKI in patients who received CM was 7.4% lower than in those who did not receive CM. This result may have been due to the lack of randomization of patients into groups, resulting in patients with CIN risk factors being placed in the group that did not receive CM.

Summary

CIN is commonly believed to be caused by CM use. However, the link between these agents' administration and the subsequent development of AKI still lacks evidence. Even though the incidence of CIN among

healthy patients is low, certain risk factors, i.e. age, or pre-existing AKI or CKD, pose a significant risk for fatal consequences. Therefore, before CM administration, especially in high-risk patients, another diagnostic method should be considered or, if necessary, low--osmolality, low-volume agents should be used.

Conflict of interest
None

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