Understanding and preventing contrast-induced acute kidney injury

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Abstract | Contrast-induced acute kidney injury (CIAKI) occurs in up to 30% of patients who receive iodinated contrast media and is generally considered to be the third most common cause of hospital-acquired AKI. Accurate assessment of the incidence of CIAKI is obscured, however, by the use of various definitions for diagnosis, the different populations studied and the prophylactic measures put in place. A deeper understanding of the mechanisms that underlie CIAKI is required to enable reliable risk assessment for individual patients, as their medical histories will determine the specific pathways by which contrast media administration might lead to kidney damage. Here, we highlight common triggers that prompt the development of CIAKI and the subsequent mechanisms that ultimately cause kidney damage. We also discuss effective protective measures, such as rapidly acting oral hydration schemes and loop diuretics, in the context of CIAKI pathophysiology. Understanding of how CIAKI arises in different patient groups could enable a marked reduction in incidence and improved outcomes. The ultimate goal is to shape CIAKI prevention strategies for individual patients.

The first report of contrast-induced acute kidney injury (CIAKI) dates back to over half a century ago[1] and prompted research that has led to more than 3,000 publications. Today, the predicted number of patients suffering from kidney damage caused by contrast media reaches the millions. CIAKI is generally considered to rank third among the causes of hospital-acquired AKI based on data from a US urban tertiary care hospital[2]. In that study, the frequency of CIAKI was surpassed only by that of AKI resulting from decreased renal perfusion (caused by volume contraction, hypotension or congestive heart failure, for example) and of medication-induced impaired renal function. If contrast media had been included in the medication category, the medication category would have been ranked second, accounting for 13% of all causes of AKI[2].

CIAKI is a major health-care problem. With more than 2 million cardiac catheterizations performed[3] and over 30 million doses of iodinated contrast medium administered annually[4], the overall harm to patients' health and the public costs associated with CIAKI are vast[5]. In light of the high risk of renal damage, the administration of contrast medium is often withheld, particularly in patients with pre-existing severe renal disease. The notion that contrast medium poses a stark challenge to the kidney is embedded in the minds of most physicians and reflected in their practice. Omitting contrast medium, however, often leads to suboptimal diagnostic information, thus compromising overall therapeutic outcome. The need to minimize risk of CIAKI must, therefore, be balanced against the need to obtain optimum imaging.

In this Review, we highlight current knowledge of the incidence of CIAKI and the underlying reasons for discrepancies between reports of CIAKI occurrence. We also discuss the pathophysiology of CIAKI, explain why patients with various pre-existing conditions respond differently to the damaging effects of contrast media, and shed light on present and future prevention strategies.

Diagnosis

A plethora of measures have been used to detect CIAKI in preclinical as well as in some clinical studies, reflecting the emergence of various novel molecular markers (such as neutrophil gelatinase-associated lipocalin (NGAL) and phosphatidylserine receptor kidney injury molecule-1 (KIM-1)), quantitative invasive methods, and functional imaging techniques to assess renal haemodynamics and oxygenation[6–10]. In routine clinical practice and in the vast majority of clinical studies, CIAKI is diagnosed by increased serum creatinine concentration within <72 h of administration of contrast media. Yet, serum creatinine, a surrogate marker for the glomerular filtration rate (GFR), is notoriously insensitive in detecting renal injury: 20% of AKI diagnosed by other biomarkers is undetected by serum creatinine measurements (so-called subclinical AKI)[11,12]. Moreover, different thresholds of serum creatinine levels are used

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Key points

- The incidence of contrast-induced acute kidney injury (CIAKI) is disputed, but clinically relevant CIAKI is less frequent than previously assumed
- Individual patient risk factors determine the mechanisms by which contrast media will induce damage to the kidney
- Pre-existing reduced renal tissue perfusion enhances the cytotoxic effects of contrast agents, which aggravate renal hypoxia; the rheological properties of contrast media have deleterious effects particularly in dehydrated patients
- Contrast medium induces apoptosis by damaging cell membranes, which increases intracellular Ca^{2+} levels, activates the pro-apoptotic unfolded protein response, decreases ATP levels and subsequently inhibits the PI3K/AKT/mTOR axis
- Volume expansion is effective in preventing CIAKI; oral hydration provides rapid short-term renal protection, whereas intravenous administration of isotonic saline offers long-lasting protection, but must be started hours before exposure to contrast agents
- Diuretics combined with servo-controlled volume infusion might provide optimum renal protection against CIAKI; urine excretion or central venous pressure can be used as set points in this context

to diagnose CIAKI: absolute increases (≥44 μmol/l or ≥88 μmol/l), percentage increases (≥25% or ≥50%) or a combination of absolute and percentage increases[13–15]. The ESUR definition of CIAKI, which was previously called contrast-induced nephropathy (CIN) (BOX 1) is the most widely used[16,17].

Detection threshold

As even small changes in kidney function might have important effects on overall outcomes, several guidelines and studies use a low threshold for changes in serum creatinine concentration to indicate CIAKI. One of the first studies to demonstrate the important effects of these minute changes in renal function on overall patient outcome and mortality was performed in 1996 (REF. 18). Patients who developed CIAKI after undergoing radiocontrast procedures had an adjusted odds ratio for mortality of 5.5. Furthermore, AKI and chronic kidney disease are clearly interconnected; even moderate AKI predisposes to chronic kidney disease, which could contribute to increased mortality after radiocontrast procedures[19,20].

From a statistical point of view, using small changes as end points bears the risk of overestimation. Using the RIFLE criteria[21] or the KDIGO definition of AKI[22] to diagnose CIAKI might reduce artefacts, as risk of renal damage is assumed for either serum creatinine increases of ≥50% or GFR decreases of ≥25%, which are both greater thresholds than those used in the conventional ESUR definition (BOX. 1). The use of different definitions and thresholds for diagnosis of CIAKI precludes direct comparison between studies. In patients undergoing percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction, only 10.4% experienced CIAKI as indicated by the KDIGO definition[23]. In a similar population, the numbers of patients with CIAKI were roughly twice as high using the conventional definition[24] (BOX. 1). Taking into account the fact that CIAKI can be subclinical, and that even minute changes in serum creatinine levels affect long-term patient outcome, a low threshold for CIAKI diagnosis seems appropriate to enable optimum patient care, even though low detection thresholds pose a problem for statistical assessment of CIAKI. False positive CIAKI-detection prolongs patient hospitalization and leads to excessively restrictive contrast medium use.

The pattern (time course) of increase in serum creatinine levels adds to the difficulties in diagnosing CIAKI. Owing to the low levels of creatinine produced by skeletal muscles and the large size of the compartments to which it is distributed (the entire water compartment), changes in serum creatinine levels lag behind actual kidney injury. The pattern of serum creatinine levels in response to CIAKI points to a sharp decline in GFR with subsequent recovery (FIG. 1). Depending on the magnitude of the sudden decrease in GFR and the subsequent recovery, peak serum creatinine levels can be very different. Thus, the narrow time-window in which serum creatinine is assessed after administration of contrast medium has been criticized[25]. The delayed rise in serum creatinine also means that CIAKI will often go undetected in outpatients.

Biomarkers

Markers such as NGAL[6,26–28], cystatin C[29,30] and KIM-1 (REF. 7) expedite detection and treatment of CIAKI, as their concentrations increase during the first hours after the insult. The shorter delay in cystatin C accumulation than in the increase in serum creatinine levels after CIAKI is mainly due to the smaller size of its distribution compartment[31]. Cystatin C remains in the extracellular space, which comprises only a third of total body water[32]. As well as being a reliable marker for early detection of CIAKI, 24 h cystatin C levels predict CIAKI severity[29].

With the emergence of these novel biochemical markers, new definitions of CIAKI based on the levels of NGAL[6,28,33] and KIM-1 (REF. 7) have been proposed. However, none of the new biochemical markers currently provide reliable point-of-care diagnosis for AKI[8]. One reason for this failure might be that these molecules are indicative of injury rather than of early signalling events in the pathophysiological chain that ultimately leads to AKI. Nevertheless, novel markers are of value in specific patients with different risk profiles, as these markers reflect the activation of diverse damaging pathways: cystatin C and creatinine levels rise in response to decreased GFR, whereas an increase in KIM-1 levels indicates proximal tubular damage[29,34] as the proximal epithelium detects and subsequently phagocytoses dead cells through KIM-1 (REF. 34). NGAL is indicative of distal nephron damage, as it is massively upregulated in the thick ascending limb of the loop of Henle, distal tubule and collecting duct[35].

The future gold standard in CIAKI diagnostics might not be found in one single biochemical marker but in a synergistic approach that includes biomarkers and functional imaging techniques[8]. Renal tissue hypoperfusion and hypoxia are pivotal elements in CIAKI pathophysiology[36–39]. Novel imaging techniques such as blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI) are, therefore, increasingly

Box 1 | **Definition of contrast-induced acute kidney injury***

- An increase in serum creatinine by more than 25% or 44 μmol/l (0.5 mg/dl)
- Within 3 days of the intravascular administration of contrast medium
- No alternative aetiology

*According to the European Society of Urogenital Radiology

used to assess impaired kidney oxygenation following administration of contrast media[40,41]. Calibration of BOLD data using methods that provide quantitative data on renal haemodynamics and oxygenation in a healthy state and in various pathological scenarios is required before BOLD-MRI can be introduced as diagnostic tool for CIAKI[9].

Epidemiology

The incidence of CIAKI is reportedly high worldwide[42,43]. In sub-Saharan Africa, between 4.6% and 16.4% of patients undergoing computed tomography (CT) scans or angiography developed CIAKI, depending on the definition used[44]. Similar incidences of CIAKI induced by intravenous administration of contrast media have been reported among patients in India (10%)[45], and among paediatric patients undergoing CT scans in Germany (10.3%)[46]. In a meta-analysis of 29 studies, in which contrast medium was given either intravenously or intra-arterially, the incidence of CIAKI was also high (4.4%-22.1%)[47]. A 2016 study suggested that contrary to previous belief that use of intra-arterial and intravenous administration of contrast medium could reduce the risk of CIAKI, both delivery modes might be associated with similar incidences of CIAKI[48].

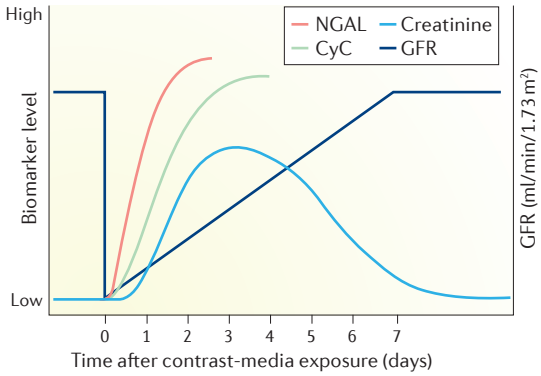

Figure 1 | **Biomarkers dynamics in contrast-induced acute kidney injury (CIAKI).** Modelling serum creatinine time courses[120] revealed a specific pattern during CIAKI, which is characterized by a sharp decline in glomerular filtration rate (GFR) followed by slow GFR recovery. Typically, serum creatinine levels peak 2–3 days after contrast medium exposure[16]. The tubular specific biomarker neutrophil gelatinase-associated lipocalin (NGAL) is particularly sensitive for the early diagnosis of acute kidney injury (AKI), including CIAKI[121], showing an increase as early as 6 h post-procedure[122]. Levels of cystatin C (CyC), an indicator of GFR, increase within 24 h after administration of contrast medium, thus constituting a further putative indicator of early stages of CIAKI[29].

Importantly, not all cases of AKI observed after administration of contrast medium are caused by the contrast agent itself. Many other risk factors for AKI including decreased renal perfusion (hypotension or atheroembolization, for example), hypoxaemia, hypovolaemia, inflammation and sepsis should also be taken into account (BOX 2). Thus, the risk of CIAKI should be calculated in relation to the overall risk of developing AKI in the hospital setting.

Importance of control groups

The many causes of hospital-acquired AKI other than administration of contrast media can only be ruled out using appropriate control groups, which have been included in very few studies of CIAKI. In a study that aimed to assess the incidence of hospital-acquired AKI in the absence of contrast media, 32,161 contrast-medium-naive patients who had undergone either radiological or cardiac procedures were identified from a clinical data set[49]. The findings were striking — contrast medium naive patients did not have a lower incidence of AKI than that reported for patients who received contrast media in most previous studies. These findings raised the question of whether contrast medium actually harms the kidney. The control group included in this study cannot, of course, be directly compared with patient groups from other studies on CIAKI and the data was not intended to be used in this way. However, the importance of control groups for assessing CIAKI more accurately is now widely recognized.

Fundamental problems exist in shaping appropriate controls for patients receiving contrast media. The main reason for performing a non-enhanced CT scan, thereby potentially forfeiting imaging quality, lies in higher risk of CIAKI. Thus, the control group can be expected to have more renal risk factors than those receiving contrast-enhanced CTs. Such selection bias can be corrected for statistically. Once the inherent differences between the control group and the group that received contrast medium were considered in the analysis, only patients with estimated GFR <30 ml/min/1.73 m^2 (REF. 50) were at risk of developing CIAKI. Subsequent similar studies failed to identify intravenous contrast medium exposure as an independent risk factor for AKI[51,52]. However, mimicking an appropriate control group statistically with propensity score models[48,51,52] requires having measured serum creatinine levels in the control group before the intervention[53]. Several patients whose serum creatinine levels are measured, and then do not receive contrast medium, will be at high-risk of developing AKI. In addition, contrast-enhanced imaging is performed for different indications than non-enhanced imaging, thus, making the two groups very different. The same imaging examination in the presence or absence of contrast agents can only be compared directly in a few instances[54].

Reassessing CIAKI incidence

The swing from considering CIAKI as a major threat to the kidney to suggesting that exposure to contrast agents does not inflict any damage to the kidney has

Box 2 | **Common risk factors for contrast-induced acute kidney injury**

- Associated with the patient
  - Concomitant acute kidney injury of other origins
  - Reduced glomerular filtration rate (<45 ml/min/1.73 m^2 or <60 ml/min/1.73 m^2 for intravenous or intra-arterial administration, respectively)
  - Previous acute kidney injury or chronic kidney disease
  - Diabetic nephropathy
  - Dehydration
  - Anaemia
  - Poor haemodynamic status
  - Age >70 years
  - Concurrent nephrotoxic drug treatment
- Associated with the procedure
  - Large doses of contrast medium
  - Multiple administrations of contrast medium
  - Use of contrast medium with excessive osmolality or viscosity
  - Intra-arterial administration (debated)

caused great controversy. Provided that effective prevention protocols, such as volume expansion and using the lowest possible dose of contrast medium, are strictly implemented[53,55], the incidence of CIAKI might be much lower than previously reported. Such prevention protocols are more rigorously adhered to in patients who receive contrast medium than in those who do not, which adds to the caution required to establish the real incidence of CIAKI. Prospective studies, but not all retrospective studies, can rule out the inconsistencies due to prevention.

Taken together, these findings show that the true incidence of CIAKI remains unclear. In addition to the confounding factors mentioned above, CIAKI occurrence varies with the risk status of populations and the amount and type of contrast medium used, as will be detailed below. For ethical reasons, comparing a group of patients receiving contrast medium without any preventive measures with appropriate control groups that do not receive any contrast medium will not be possible. Nonetheless, many studies published in the past 5 years showed that the incidence of CIAKI is lower than previously reported, as several other causes of AKI were not fully accounted for. Notably, a registry study that included 57,925 patients receiving contrast medium reported clinically relevant renal failure in only 0.8%–1.7% of patients[56].

Renal susceptibility to contrast media

After injection, contrast media become considerably diluted within the bloodstream (their initially very high viscosity and osmolality greatly decrease) (FIG. 2; TABLE 1). Thus, all non-renal organs are exposed to low concentrations of contrast agents with some exceptions. During coronary interventions, for example, heart vessels are exposed to high concentrations of contrast medium, due to local administration into the coronary arteries. Contrast medium is exclusively eliminated by the kidney. After being filtered at the glomeruli, contrast medium is not reabsorbed by the tubules. As a result, the concentration of the contrast agent rises on the way through the tubules (FIG. 2).

Hand-in-hand with the increase in contrast medium concentration, renal exposure to this agent is prolonged owing to increased tubular fluid viscosity. Concentration–viscosity relationships are exponential. Thus, tubular fluid containing contrast medium becomes increasingly viscous towards the distal nephron segments[57] (FIG. 2). Any increase in fluid viscosity reduces flow rate for a given pressure gradient. Thus, renal tubular congestion can occur, depending on the dose and the physicochemical properties of the contrast medium and hydration status of the patient. These tubulodynamics and the distinctive blood supply to the kidney require particular consideration in the setting of CIAKI. Damage induced by contrast medium includes general processes, such as apoptosis (FIG. 3; BOX 3), but the triggers of such damage can vary.

Hypoperfusion and hypoxia

Pre-existing risk factors such as disorders with endothelial dysfunction, including diabetes mellitus, determine the importance of the pathophysiological mechanisms of CIAKI at play in each individual[36,37]. In the setting of endothelial dysfunction, impaired glycocalyx function and compromised flow-mediated nitric oxide production might render the endothelium susceptible to further damage by contrast media[38,58]. As shown by electron microscopy, even moderate doses of contrast media damage the endothelial surface[59]. Endothelial dysfunction, as seen in diabetes mellitus, can be emulated in rats by inhibition of nitric oxide and prostaglandin production[60]. In this model, renal oxygenation is reduced after the administration of contrast medium, as shown by BOLD-MRI. Endothelin-1-mediated vasoconstriction might have a role in this setting as, in addition to increased endothelin-1 activity in patients with diabetes mellitus, endothelin-1 is released upon exposure to contrast medium[61]. A vicious circle might develop in which cytotoxic effects on renal tubular and vascular endothelial cells cause tissue hypoperfusion and hypoxia, which, in turn, aggravate the initial tissue damage caused by contrast medium.

Reduced tissue oxygenation, medullary hypoxia in particular, is a hallmark of CIAKI[36–39]. Medullary hypoxia contributes to the vicious circle leading to cellular damage, oxidative stress and vasoconstriction. Contrast medium affects the balance between medullary oxygen delivery and consumption by constricting the long and narrow vasa recta, which is a major source of blood supply to the medulla. Indeed, pericytes surrounding the vasa recta contract when exposed to contrast medium[62]. In a series of *in vitro* studies in isolated vasa recta obtained from rats and humans, contrast medium applied to the lumen led to constriction and enhanced vasa recta responses to angiotensin II[59,63]. In these studies, vasa recta were perfused with crystalloid solutions that contained contrast agents in low concentrations so that the osmolalities and viscosities of the solutions equalled that of plasma. Contrast media of all classes caused similar degrees of vasa recta constriction[64].

Tubulovascular crosstalk is mediated by reactive oxygen species (ROS) among other mediators, which might be involved in CIAKI. In a double perfusion

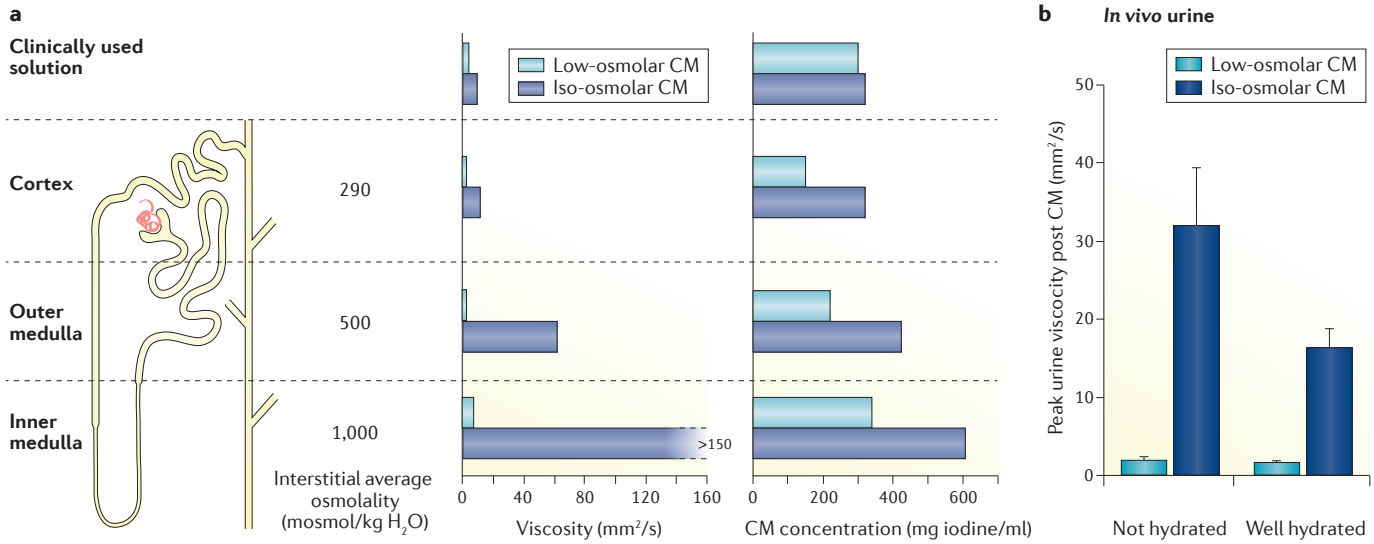

Figure 2 | **Determinants of renal contrast medium enrichment. a** | Contrast media (CM) are not reabsorbed so they become concentrated en route through the tubules. Conversely, interstitial osmolality drives tubular water reabsorption. The effects of these osmotic forces on CM concentration and viscosity were modelled by *in vitro* dialysis of CM solutions[57]. At the ambient osmolality of 290 mosmol/kg H_2O, the concentration of CMs with high osmolality (that is low-osmolar CMs when compared to iso-osmolar CMs, see also TABLE 1) decreased owing to water inflow. With increasing ambient osmolalities, water is progressively extracted from the solutions and fluid viscosity increases. At 1,000 mosmol/kg H_2O, the concentration of low-osmolar CM is slightly elevated whereas that of iso-osmolar CM is about twice as high as that of their original solutions. Owing to the exponential concentration–viscosity relationship, the viscosity of the iso-osmolar CM solution markedly exceeds that of the original solution as it was higher than the maximum value that the viscometer could measure in this experimental setting (150 mm^2/s)[57]. **b** | *In vivo*, all contrast agents induce osmodiuresis to the degree of their osmolality. Consequently, in a rat model, tubular CM enrichment is higher, and urine viscosity much higher, following iso-osmolar versus low-osmolar CM administration[84]. These differences in the magnitude of tubular CM concentration and viscosity are inversely related to the hydration status.

model of the thick ascending limb and the afferent arteriole, contrast medium administration aggravated vasoconstriction in response to sodium chloride loading at the macula densa[65]. This so-called sensitized tubuloglomerular feedback, together with increased angiotensin II reactivity of the afferent arterioles, contributes to the fall in GFR in CIAKI[65,66]. The motility of afferent arterioles and vasa recta were similarly affected by tubulovascular crosstalk[62,67]. Signals from injured tubular epithelia could therefore cause vasa recta vasoconstriction.

In vivo, contrast medium increases the viscosity of the blood flowing through the medulla[68], which can severely damage the endothelial surface mechanically or through cytotoxic effects[59], thus aggravating endothelial dysfunction. Successful strategies to prevent CIAKI might therefore involve targeting the endothelium. For example, adrenomedullin, an endogenous peptide with endothelium-protective properties, protects the endothelial cell surface in contrast-medium-perfused interlobar arteries and restores vasa recta responsiveness[59].

Lastly, contrast agents increase tubular pressure, leading to compression of the vasa recta, which intensifies renal hypoxia induced by contrast medium administration[41,68]. In addition, osmodiuresis resulting from hyperosmolar contrast medium might increase the workload in the distal nephron segments, which are then at risk of damage in CIAKI. Sodium cannot fully bind to water that is already bound to contrast agents. Osmodiuretics, such as mannitol and contrast media, decrease the concentration of sodium chloride at the macula densa[69], but increase tubular flow. Thus, if any enhanced sodium load to distal nephron segments were to occur, its effects would be smaller than the diuretic effect of contrast medium.

Cell damage and apoptosis

Diverse CIAKI pathways, such as hypoxic damage or ROS generation, converge into a common downstream damaging mechanism. Thus, assessing the initial triggering event can be difficult. In *in vitro* studies, all contrast media are potentially cytotoxic at high concentrations, as shown by reduced cell viability[70]. In line with an assumed direct cytotoxic effect of contrast media, experiments using very diluted contrast agents to perfuse organs showed damage to the kidney[65,59]. In that setting, haemodynamics remain largely unchanged and hypoxia does not occur. Thus, the damage is related to the substance itself.

Direct cell toxicity of contrast media is initiated by cell membrane damage, as indicated by cytoplasmic vacuolization and loss of the membrane proteins caveolin and Na^+/K^+-ATPase[71,72]. However, the induction of invaginations in proximal tubular cells following contrast medium administration *in vivo* might be associated to hypoxia or fluid viscosity[73,74]. Nevertheless,

Table 1 | **Properties of commonly used radiocontrast media**

Type*	Structure	Example (generic name)	Iodine concentration (mg I/ml)†	Osmolality (mosmol/kg H_2O)†	Viscosity (Pa·s at 37 °C)†
High osmolar	Ionic monomer	Sodium iothalamate	325	1,843	0.00275
Low osmolar	Non-ionic monomer	Iopamidol	300	636	0.00525
Iso-osmolar	Non-ionic dimer	Iodixanol	320	290	0.0114

Most compounds are marketed in solutions with various iodine concentrations (150–370 mg I/ml for iopamidol, for example); the osmolality and viscosity of solutions of a given compound increase with the solution's iodine concentration. Intravascular use includes diagnostic and interventional cardiac and coronary procedures, arteriography and angiography of various vascular beds, intravenous contrast-enhanced computed tomography, and intravenous urography. *For historical reasons, radiocontrast media are classified according to the osmolality of their solutions. †Data from the manufacturers.

addition of contrast medium to HK-2 cells (a proximal tubular cell line derived from human kidney) causes membrane disruption, a marked decline in adenosine triphosphate (ATP) levels, elevated adenosine levels and a dramatic loss of cytochrome c[72]. These initiating effects trigger stress-related pathways including activation of p38 and JNK mitogen-activated protein kinases, NF-κB and ROS signalling, along with inhibition of cAMP, phosphoinositide 3-kinase (PI3K), RAC-β serine/threonine-protein kinase (AKT), mTOR, extracellular signal-regulated kinase (ERK) 1 and ERK2, cyclic AMP-dependent transcription factor ATF2 and the forkhead box O protein family, which eventually lead to apoptosis[70]. From the pathophysiological viewpoint, the outer medullary tubular cells undergo the most extensive damage and predominantly suffer from the effects of hypoxia[74]. These nephron segments are also exposed to particularly high concentrations of contrast medium.

In vitro studies documented apoptosis, identified by nuclear fragmentation, increased annexin V staining, and activation of caspase-3 and caspase-9, after contrast medium administration[75]. Other studies reported that contrast agents reduced the expression of the anti-apoptotic factor apoptosis regulator Bcl-2 and increased expression of the pro-apoptotic factors apoptosis regulator BAX, Bcl2-associated agonist of cell death (BAD) and Bcl-2-like protein 11 (encoded by *Bim*)[75,76]. Although the complex interplay of the molecular pathways that lead to contrast medium-induced apoptosis has become clearer, the molecular mechanisms involved in the final steps that result in apoptosis remain elusive. In 2003, a crucial observation shed light on the final prompting of contrast medium-induced apoptosis: elevated intracellular levels of Ca^{2+} were required for cell injury after contrast agent exposure in microvascular endothelial cells[77]. Accordingly, apoptosis was prevented by chelating intracellular Ca^{2+}, but not by removing extracellular Ca^{2+}. Increased intracellular Ca^{2+}, caused by leakage from the endoplasmic reticulum (ER), enhanced mitochondrial Ca^{2+} uptake and induced cytochrome *c* release, thereby activating cytochrome *c*-dependent apoptosis[72]. Such processes triggered the unfolded protein response (UPR) pathway, which is the predominant adaptive response to ER stress and is crucial for cellular adaptation and maintenance of proteostasis[78]. Albeit the UPR is known as a pro-survival response, this 'adaptive' UPR pathway is overcome by severe and/or long-term ER stress. Under such conditions, the 'pro-apoptotic' UPR pathway becomes dominant[78]. In line with these observations, activation of the UPR was found in a rat renal tubular cell line (NRK52E) exposed to contrast medium[79], and *in vitro* studies published in 2014 and 2015 reported protective effects of ER-stress inhibition in contrast medium-induced apoptosis[80,81].

Taken together, the direct cell toxicity induced by contrast medium seems to rely on cell membrane damage, intracellular Ca^{2+} release, activated pro-apoptotic UPR, ATP decline, reduced cAMP signalling and subsequent inhibition of the PI3K/AKT/mTOR axis that, in turn, all activate pro-apoptotic pathways. The destabilization of membranes, including mitochondrial and plasma membranes, might be the primary cause of direct cellular damage induced by contrast agents. Whether the release of inorganic iodide from contrast agents and its subsequent toxicity is involved in cellular damage is under debate[72].

Disturbed tubulodynamics and glomerular filtration

Rheological effects of contrast medium can slow fluid flow through the tubules and intrarenal blood perfusion; such reduced flow velocities dramatically enhance renal exposure to contrast medium. In a well hydrated state, these rheological effects are small, which might explain why well controlled randomized trials failed to provide evidence of differences in the incidence of CIAKI with respect to the type of contrast medium[4].

In vivo studies suggest that the physicochemical properties of contrast agents affect the magnitude of tubulodynamic and renal haemodynamic changes and account for their damaging potential[7]. The pioneer class of contrast media consists of ionic monomers with extremely high osmolalities (TABLE 1). A second generation of contrast media comprises non-ionic monomers with lower osmolalities. Finally, in the third generation of contrast media, iso-osmolarity was achieved by creating non-ionic dimeric compounds[82]. The low osmolality reached with the latest generation of contrast media came at the price of considerably increased viscosity, which is thought to rely on the shape of the molecule and the flexibility of the bridge between the two benzene nuclei that might lead to their superposition[83].

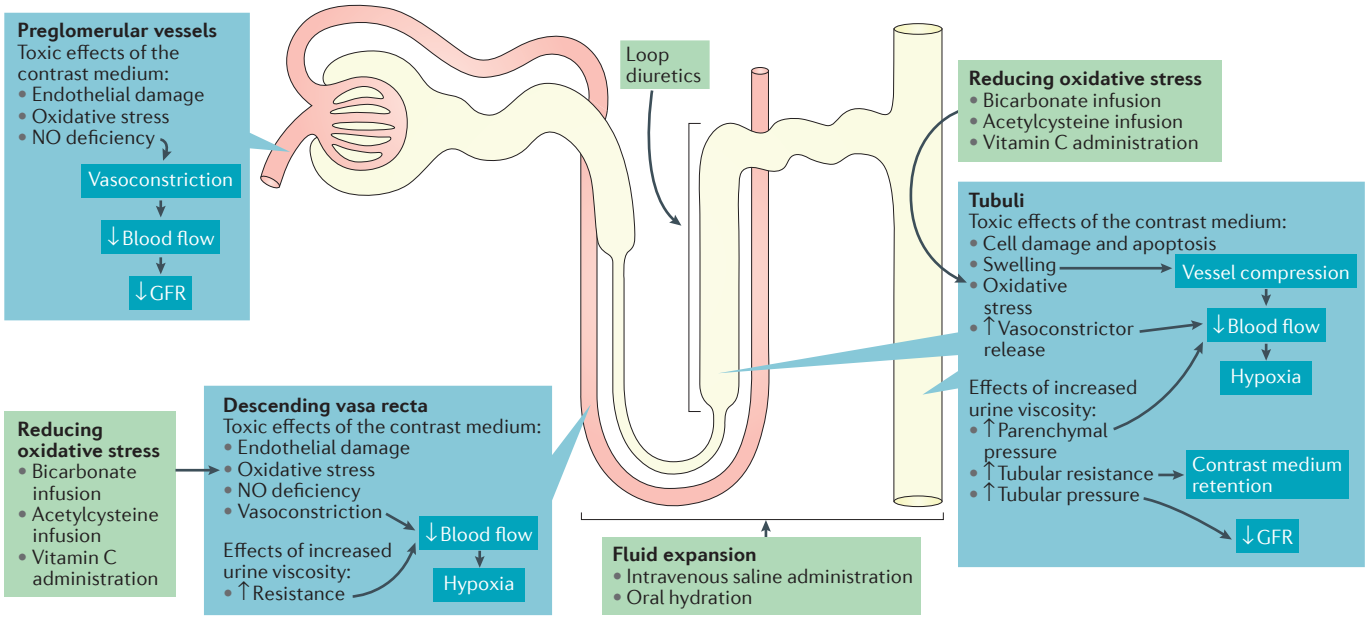

Figure 3 | **Pathophysiological events and preventive strategies in contrast-induced acute kidney injury (CIAKI).** Contrast agents damage several components of the kidney (blue boxes). Contrast medium toxicity induces membrane damage in epithelial and endothelial cells. Endothelial dysfunction and vasoactive substances released from epithelial cells cause vasoconstriction. Afferent arteriolar constriction results in a rapid decrease in glomerular filtration rate (GFR)[67]. The outer medulla is at risk of CIAKI owing to its high metabolic demand and comparatively low perfusion via the vasa recta[74]. The latter constricts when exposed to contrast medium[59]. Concomitant cell damage takes place owing to hypoxia, initiating apoptosis and aggravating renal hypoperfusion by cell oedema and further vasoconstriction. Concentration of contrast medium in the tubules and vasa recta increases fluid viscosity, which compromises urine and blood flow[84], thus decreasing GFR and oxygenation, and prolonging contrast medium exposure. Strategies for prevention of CIAKI such as fluid expansion and decreasing oxidative stress are based on pathophysiological knowledge (green boxes). NO, nitric oxide.

In the dehydrated individual, the elimination of contrast medium can lead to tubular congestion, as the bulk of filtered volume is reabsorbed leaving behind highly concentrated viscous contrast medium in the remaining fluid[10,84]. Tubular pressure, measured by micropuncture in rats, is particularly high following infusion of highly viscous contrast media[68]. This high tubular pressure lowers GFR. Indeed, marked transient decreases in GFR take place following administration of highly viscous contrast media[84]. Studies using functional MRI confirmed that tubular fluid viscosity depends on the physicochemical properties of the contrast agent used[85–87].

In analogy to tubulodynamics, blood perfusion of the hypertonic medullary environment is affected by contrast agents in plasma. In a high osmotic environment, plasma water exits the vascular lumen towards the interstitium, causing enrichment of the contrast agent in the vasa recta, thus increasing local blood viscosity and local vascular resistance[10].

Contrast medium administration leads to a rather small increase in urine viscosity in well hydrated patients, dogs and rats[10,57,73,84–86,88–90]. Conversely, pronounced increases in urine viscosity are found in freely drinking rats, which concentrate their urine to an extent comparable to non-hydrated humans[84]. These findings are not surprising as the degree of tubular water reabsorption and, thus, the degree of contrast agent enrichment in the tubular fluid, depend on hydration and volume statuses. Even minor increases in tubular water reabsorption will greatly increase tubular fluid viscosity owing to the exponential relationship between concentration and viscosity (FIG. 2). This relationship explains that insufficiently hydrated patients have a much higher risk of CIAKI and provides a rationale for the strong recommendation for ample hydration included in all current clinical guidelines for intravascular contrast medium administration[16,17]. In the dehydrated state, osmodiuresis caused by a contrast agent of moderately high osmolality (so-called low osmolar contrast media (TABLE 1)) might counteract excessive urine viscosity levels[73,84,89].

Preventative strategies

CIAKI prevention strategies target the various pathophysiological mechanisms of contrast-medium-induced renal damage (BOX 4); however, strategies that do not include volume expansion, usually fail[91]. Common strategies besides decreasing fluid viscosity in the tubules and vessels include reducing oxidative stress, preventing local hypoxia and alleviating inflammatory responses. Outcomes of these strategies are of vast clinical interest and have been reviewed extensively elsewhere[92]. Here, we focus on fundamental concepts underlying the strategies behind the intense preventive measures required by patients at high risk of CIAKI and the challenges they present.

Box 3 | **Renal damage induced by contrast agents**

- Cellular effects
  - Direct cell membrane damage
  - Perturbation of mitochondrial function
  - Generation of reactive oxygen species
  - Apoptosis
- Hypoxia and vasoconstriction
  - Constriction of afferent arterioles and/or vasa recta
  - Enhanced renal vascular responsiveness to angiotensin II and endothelin-1
  - Endothelial damage with subsequent vasoconstriction
  - Increased vascular resistance by congestion
  - Acute hypotension (anaphylaxia)
- Tubular effects
  - Perturbed tubuloglomerular feedback
  - Cytotoxic effects
  - Tubulovascular crosstalk with subsequent vasoconstriction
  - Tubular obstruction by increased fluid viscosity

Reducing oxidative stress

Bicarbonate infusions, acetylcysteine and vitamin C administration are only a few examples of the attempts to reduce local oxidative stress induced by contrast agents in the kidney. Despite the numerous studies and meta-analysis, the outcomes of these treatments remain disputed[92]. Reducing oxidative stress should take place in the particular area of the kidney that is at risk of CIAKI. For example, animal studies reported that the combined administration of contrast medium and various other noxious agents damaged the inner and outer medulla (medullary thick ascending limb of the loop of Henle and S3 segment of the proximal tubule)[74]. Thus, antioxidative measures should be directed to the zones of the kidney where they can prevent damage.

Na^+-coupled HCO_3^- transport mainly takes place in the S1 segments of the proximal tubules (which are adjacent to the Bowman capsule) and early S2 segments[93]. Owing to its early reabsorption, bicarbonate concentration in the S3 segment is only 20% of that found in the plasma[94]. Little bicarbonate is left in the aforementioned areas at risk of CIAKI, although bicarbonate subsequently becomes more concentrated owing to water uptake in the collecting ducts. Remarkably, proximal tubules also produce bicarbonate[94], which might not only be important for neutralizing mineral acids, but also for alleviating damage caused by contrast media. Infusing bicarbonate could reduce new bicarbonate formation in the proximal tubule, adding to diminished tubular delivery of bicarbonate to the area damaged by contrast agents. These processes might explain why bicarbonate administration has not been shown to be consistently effective[92,95,96]. Bicarbonate does eliminate acids in the proximal tubules and can be active much further downstream in preventing certain kidney stones. Unless bicarbonate is delivered to the areas at risk of CIAKI via blood flow, no preventive effect of bicarbonate administration against CIAKI can be expected.

Loop diuretics
Diuretic agents that act on the thick ascending limb of the loop of Henle to inhibit sodium, chloride and potassium reabsorption.

Diuretics

Loop diuretics such as furosemide have long been considered to aggravate CIAKI[97,98]. Nonetheless, trials published in 2011 and 2016 showed that furosemide administration after contrast agent exposure is safe[99] and effectively prevents CIAKI development[100]. Determining the specific protective effect of furosemide administration against CIAKI from the overall published studies on furosemide[101] is difficult. Patients receiving large amounts of contrast medium are often those undergoing complex procedures, such as PCI, and are not representative of the general population.

In the light of the pathophysiological mechanisms that cause CIAKI, patients should benefit from periprocedural administration of diuretics. High urine flow reduces exposure to contrast medium in a linear fashion. Moreover, increased urine flow decreases tubular fluid viscosity exponentially[57], and furosemide might lower oxygen demand in the medullary thick ascending limbs (mTAL) of the loop of Henle, which are at risk of CIAKI. Early preclinical studies support the notion of furosemide being protective against contrast agent exposure[102], but furosemide was subsequently shown to have deleterious effects in the clinical setting[97]. In rats, the mTAL morphology was remarkably preserved with furosemide treatment and fluid replacement[102]. Conversely, furosemide-treated rats without fluid replacement had profound mTAL collapse, presumably reflecting reduced GFR in superficial nephrons and enhanced proximal tubular transport[102]. Thus, prerenal causes such as volume depletion could explain the deleterious effects of furosemide. A 1992 study reported that patients given furosemide lost ~>1 l of volume[97]. In a 1994 trial[98], such high volume loss was not reported, but in the early days of PCI, urine flow rates were extremely high owing to high dosing of contrast agents and use of ionic high osmolar contrast media in one third of cases. Initial urine production could have escaped collection while patients were being catheterized and placed on the intervention table. Taken together, trials in which patients treated with furosemide acutely lost weight (an indicator of volume loss) showed worse outcomes associated with CIAKI than trials in which such weight loss was not observed.

Negative fluid balance stimulates the renin–angiotensin–aldosterone system leading to enhanced tubular water reabsorption, thereby increasing tubular fluid viscosity, and to renal vasoconstriction[101]. These factors might explain the negative CIAKI outcome in some studies that used loop diuretics. If fluid losses are promptly replaced, with an automatic replacement device for example, furosemide does indeed reduce the incidence of CIAKI[100,103].

Oral versus intravenous fluid expansion

Unequivocally, only volume expansion performed before a procedure reduces the incidence of CIAKI, limits its severity and improves overall outcomes[104]. However, hydration in patients with heart or kidney

disease comes at a risk. Excessive volume expansion might cause more harm than benefit[105] in settings such as heart failure. Servo-controlled replacement is the optimum way to maintain protection and to avoid excessive volume expansion[99]. Various set points can be used to adjust volume expansion: urinary flow for balancing fluid volume[99], central venous pressure to maintain constant preload to the heart[106], or left ventricular end diastolic pressure[107]. In general, total body water parallels effective intravascular fluid volume, which is a decisive measure for stratifying CIAKI risk[108]. The former can be assessed by bioimpedance vector analysis[108], which might provide a further set point for balancing fluids.

Guidelines for prevention of CIAKI put forward volume expansion by rigid long-term saline infusions[16], which are better controlled and, thus, superior to simply not restricting oral fluid intake[109]. According to guidelines[16,17], intravenous infusions should start 6–12 h before the intervention and be maintained for 4 h after the intervention. For hospitalized patients, this strategy is a feasible way to achieve reliable volume expansion. However, many of the >30 million patients per year who receive contrast medium cannot undergo volume expansion according to such protocols. In the real-life setting in which an outpatient arrives for a CT scan, prehydration has often not taken place. In fact, the patient is often dehydrated at the time of exposure to a contrast agent. In such situations, oral hydration using tap or mineral water might bear the specific advantage of inducing a rapid increase in urine flow.

The protective effects of oral hydration and intravenous saline administration are ultimately probably identical; the contrast medium is effectively diluted in the medullary region, thus minimizing exposure of the tubular epithelial cells and vasa recta. Moreover, urine viscosity decreases, which prevents tubular obstruction and expedites the elimination of the contrast agent. Yet, fundamental differences between oral hydration by water (or other hypotonic fluids) and intravenous isotonic saline exist regarding the regulatory mechanisms to enhance renal water excretion (FIG. 4).

Box 4 | **Measures to prevent contrast-induced acute kidney injury**

- Limit exposure
  - Consider alternative imaging methods not requiring contrast medium
  - Use the lowest dose of contrast medium that enables a diagnostic result to be established
  - Avoid multiple administrations of contrast medium within a few days
  - Prevent renal congestion by hydration or volume expansion
  - Diuretics (debated)
- Scavenging reactive oxygen species (debated)
  - Acetylcysteine administration
  - Bicarbonate infusion
  - Vitamin C administration
- Decrease local renal oxygen demand or enhance local oxygen supply (debated)
  - Loop diuretics administration
  - Vasodilator use
  - Administration of angiotensin-converting enzyme, angiotensin II inhibitors and endothelin-1 antagonists

The diuretic response to oral water intake involves osmoregulatory mechanisms that, by suppressing vasopressin release, lead to rapid diuresis. As isotonic saline does not alter blood osmolality, saline triggers different volume-control mechanisms, in particular, suppression of the renin–angiotensin axis. The renal response to intravenous administration of isotonic saline takes longer than that elicited by oral water hydration, which enhances urine flow after only a few minutes. Similar to intravenous saline, the diuretic response to oral intake of isotonic saline is delayed. A pilot study to compare the effect of oral salt and water versus intravenous saline on the prevention of CIAKI is ongoing[110].

Although oral water hydration acts rapidly, its effects are short-lived. Therefore, oral hydration should be continued after the intervention or be merely used to prompt vasopressin inhibition before saline intravenous infusion. Few clinical trials have tested the effectiveness of oral hydration with tap water or mineral water for prevention of CIAKI[111,112]. A meta-analysis of six studies on oral hydration[113] addressed this question and found that oral volume expansion with water does protect against CIAKI. Taken together, current clinical evidence suggests that the oral route for volume expansion is at least equally effective as intravenous saline for preventing CIAKI, but studies with greater power performed on patients at high risk of CIAKI are required.

Alternative radiocontrast agents

Reducing exposure to contrast agents is the best strategy for prevention of CIAKI. Nonetheless, open questions remain, such as the minimum safe dose range or whether a threshold dose exists. Using alternative contrast agents might help to further reduce exposure. Carbon dioxide (CO_2) has been used for quite some time as a negative contrast agent[114,115]. With the advent of digital subtraction techniques in the 1980s, CO_2 evolved into a useful contrast agent for vascular imaging in both the arterial and venous circulations[114,115]. Thus, CO_2 is used in a variety of clinical settings, sometimes as a stand-alone contrast agent, or as a supplement to iodinated contrast medium[114,116,117]. Unfortunately, use of CO_2 as alternative contrast agent to image the thoracic aorta, the coronary arteries, and the cerebral arteries in patients with renal failure or with allergy against iodinated contrast medium is limited by contraindications related to the risks of inducing cardiac arrhythmia, myocardial infarction, and potential neurotoxicity[115]. Furthermore, CO_2 requires a special delivery system to prevent air contamination and gas compression.

Contrast media with high atomic number elements such as hafnium, tungsten and krypton have high absorption in the X-ray energy spectrum of CT for adults, which enables practicians to reduce the radiation dose for these patients while maintaining the diagnostic image quality[118,119]. Whether or not these novel compounds are safer for the kidney than iodinated contrast media remains to be studied.

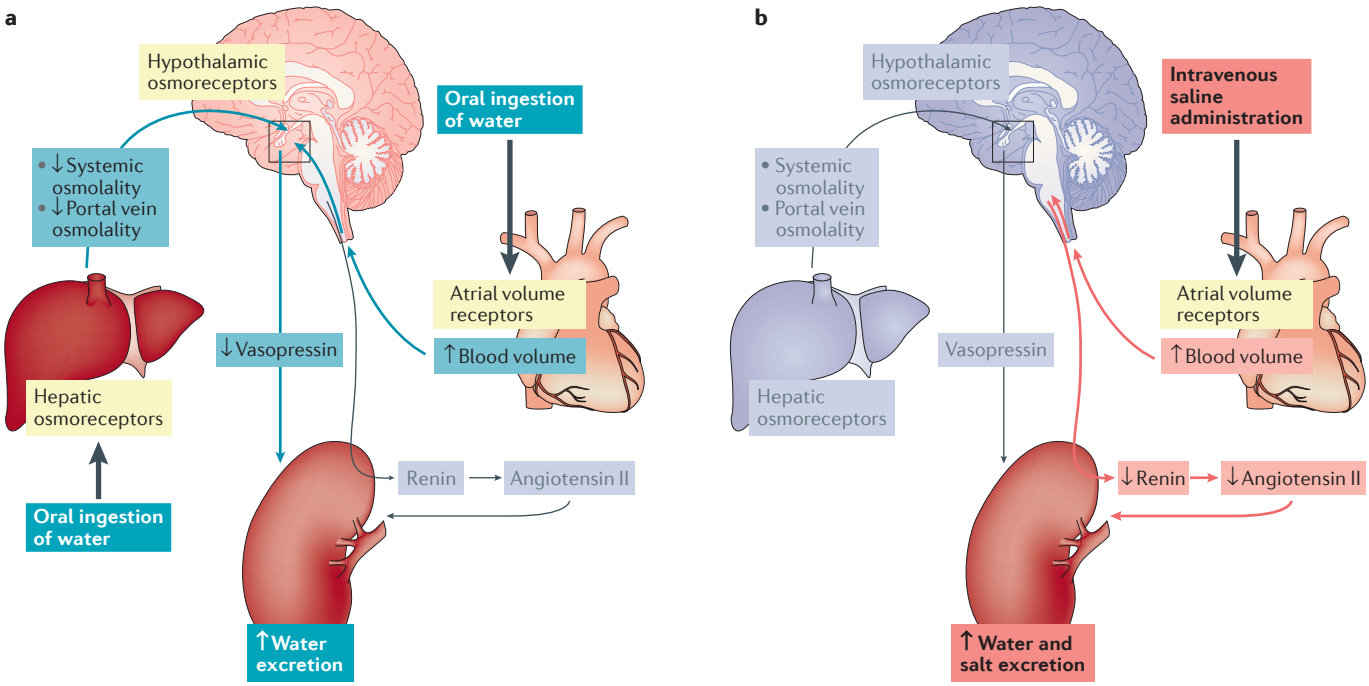

Figure 4 | **Differential protective effects of hydration and volume expansion according to administration route and fluid use. a** | Oral water ingestion decreases osmolality and increases blood volume, which promptly suppresses vasopressin release from the pituitary gland[123]. Hypothalamic and hepatic osmoreceptors sense osmolality. Vagal afferences project the signals from hepatic osmoreceptors and cardiac volume receptors to the hypothalamus, which accelerate vasopressin suppression. The latter reduces water reabsorption in the collecting ducts, thus eliciting diuresis[123]. **b** | Isotonic saline, given orally or intravenously, does not change blood osmolality. Thus, no rapid osmoreceptor response occurs (which is the major reason behind the delayed response to saline). Saline loading increases the excretion of both water and sodium. As vasopressin controls tubular water reabsorption but not sodium reabsorption, it does not have an important role in the response to saline loading. Saline loading suppresses the renin–angiotensin–aldosterone system[124], which relies, in part, on the signals of the atrial volume receptors. Low levels of angiotensin II increase renal sodium and water excretion by its direct effects on tubular reabsorption. Low aldosterone levels help to promote sodium excretion, but aldosterone effects are considerably delayed.

Conclusions

Adherence to prevention protocols has likely resulted in a reduction in the incidence of clinically relevant CIAKI. Moreover, in early studies, low detection thresholds of serum creatinine levels and the lack of control groups probably led to an overestimation of CIAKI incidence. Improved understanding of CIAKI pathophysiology has increased the appreciation of how the importance of different damaging pathways varies with individual risk factors. In patients with pre-existing compromised renal perfusion, direct effects of contrast agents on renal tubular and vascular endothelial structures might have a predominant role, as all contrast agents aggravate renal hypoperfusion and hypoxia. In patients with pre-existing endothelial dysfunction such as those with diabetes, CIAKI might result from aggravation of this dysfunction. By contrast, in dehydrated individuals the kidneys might primarily be harmed by rheological effects of contrast media, which perturb tubulodynamics and renal haemodynamics. Many damaging pathways can merge into a common final route leading to CIAKI: cell membrane damage causes Ca^{2+} release, activating the pro-apoptotic UPR, and ATP loss leads to subsequent inhibition of the PI3K/AKT/mTOR axis.

Effective prevention of CIAKI includes generous volume expansion to expedite the elimination of the contrast agent and to avoid obstruction of the distal nephron segments and vasa recta. Oral hydration with hypo-osmolar fluid is a rapid way to prevent concentration of the contrast agent in these vascular and tubular compartments. However, long-lasting dilution of contrast medium requires continuous drinking or intravenous volume loading. Loop diuretics can be very effective, particularly when volume loss is replaced by a servocontrol device[99,100].

Contemporary contrast media are extremely well tolerated agents. Developing contrast media with even better renal safety profiles is possible by considering fluid viscosity as a primary damaging factor. The incidence of CIAKI will decrease dramatically when volume expansion protocols are implemented worldwide. Given the protective effect of 'diluting' contrast medium in the tubules, pre-hydration should be considered in all patients. The recommendation of 'nil per os after midnight' (nothing through the mouth after midnight) before a planned X-ray examination should, therefore, be reconsidered.

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