Kidney & Blood Pressure Research

Kidney Blood Press Res 2020;45:131–141
DOI: 10.1159/000504547
Received: September 4, 2019
Accepted: November 1, 2019
Published online: December 20, 2019

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Research Article

The Effect of Urine pH and Urinary Uric Acid Levels on the Development of Contrast Nephropathy

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Keywords
Contrast nephropathy · Uric acid · Urine uric acid · Acute kidney injury

Abstract
Background: Hyperuricemia may cause acute kidney injury by activating inflammatory, pro-oxidative and vasoconstrictive pathways. In addition, radiocontrast causes an acute uricosuria, potentially leading to crystal formation. We therefore aimed to investigate the effect of urine acidity and urine uric acid level on the development of contrast-induced nephropathy (CIN) in patients undergoing elective coronary angiography. ***Methods:*** We enrolled 175 patients who underwent elective coronary angiography. CIN was defined as a >25% increase in the serum creatinine levels relative to basal values 48–72 h after contrast use. Prior to coronary angiography and 48–72 h later, serum uric acid, urea, creatinine, bicarbonate levels, and spot uric acid to creatinine ratio (UACR) were measured. ***Results:*** Of the 175 subjects included, 29 (16.6%) developed CIN. Those who developed CIN had a higher prevalence of diabetes, higher UACR (0.60 vs. 0.44, p = 0.014), higher contrast volume, and lower serum sodium level. With univariate analysis of a logistic regression model, the risk of CIN was found to be associated with diabetes (p = 0.0016, OR = 3.8 [95% CI: 1.7–8.7]), urine UACR (p = 0.0027, OR = 9.6 [95%

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CI: 2.2–42.2]), serum sodium (p = 0.0079, OR = 0.8 [95% CI: 0.77–0.96]), and contrast volume (p = 0.0385, OR = 1.8 [95% CI: 1.03–3.09]). In a multiple logistic regression model with stepwise method of selection, diabetes (p = 0.0120, OR = 3.2 [95% CI: 1.3–8.1]) and UACR (p = 0.0163, OR = 6.9 [95% CI: 1.4–33.4]) were the 2 risk factors finally identified. ***Conclusions:*** We have demonstrated that higher urine UACR is associated with the development of CIN in patients undergoing elective coronary angiography.

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Introduction

Contrast-induced nephropathy (CIN) was historically a common cause of acute kidney injury (AKI) in hospitalized patients following surgery and hypotension [1, 2] with a significantly increased risk of mortality in short- and long-term follow-up [3]. Early studies linked contrast nephropathy with the use of high-osmolality contrast media, and biopsy studies documented a tubular lesion that resembled osmotic nephrosis [4]. Indeed, experimental studies have also identified the increased osmolal load of radiocontrast as a means for inducing the aldose reductase-fructokinase pathway in the proximal tubule, resulting in oxidative stress and tubular injury [5]. The use of low-osmolarity contrast media (which is still high relative to serum osmolality) has resulted in a lower frequency of AKI, and this has been further reduced with protocols that include minimizing the volume of contrast administered and providing hydration. As a consequence, the frequency of CIN is low [6] and likely overestimated [7]. Additionally, many clinical studies demonstrated that several novel renal biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and antithrombin III, might predict CIN earlier than serum creatinine [8–10].

Nevertheless, our group continues to see cases of AKI following radiocontrast administration, and we and others have shown that the injury can be predicted by the presence of hyperuricemia [1, 11]. Hyperuricemia activates inflammatory, pro-oxidative, and vasoconstrictive pathways and has been implicated in both acute and chronic kidney injury [12–16]. In addition, radiocontrast also may cause an acute uricosuria [17, 18], potentially leading to crystal formation, especially if the urine is acidic [19]. Focusing on this latter observation, we decided to test the hypothesis if urine acidity, urine uric acid level, serum bicarbonate, and serum uric acid level might be risk factors for the development of CIN in patients undergoing elective coronary angiography.

Materials and Methods

Patients and Study Design

Koc University School of Medicine ethics committee approved the study protocol. We enrolled 175 patients who were admitted to the Cardiology Department of Koc University Hospital for elective coronary angiography between January 2018 and December 2018. Data was collected prospectively regarding clinical, demographic, and laboratory findings of the patients. Patients who were older than 18 years and had an estimated glomerular filtration rate (eGFR) between 30 and 90 mL/min/1.73 m^2 (according to the CKD-EPI formula) were included in this study. Written informed consent was obtained from all subjects before enrollment. Patients meeting the following criteria were excluded: age older than 80 years, dialysis patients, stage 5 chronic kidney disease, eGFR >90 mL/min/1.73 m^2, stage 4 heart failure, cardiogenic shock related to myocardial infarction, history of gout, ongoing allopurinol treatment, ongoing glomerulonephritis treatment, or diagnosis of cancer.

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CIN was defined as a >25% increase in the serum creatinine levels relative to basal values 48–72 h after contrast use. The patients were divided into 2 groups based on changes in the serum creatinine values 48–72 h after contrast use. Patients with ≥25% increase in the serum creatinine values were categorized as CIN, while patients with no change or <25% increase in the serum creatinine values were included in the control group. We also stratified subjects as control, subclinical AKI, or CIN based on the more sensitive biomarker of AKI, NGAL.

The amount of contrast and the medications used by the patients were recorded with the demographic characteristics and all other clinical data of the patients involved in this project. To help prevent the development of CIN, the use of nephrotoxic drugs, such as non-steroid anti-inflammatory drugs, metformin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics, was stopped and hydration was given to patients following published guidelines [2]. In addition, N-acetylcysteine (>1,200 mg/day) was given to all patients starting 2 days before coronary angiography and continuing until 2 days after angiography.

Biochemical Analyses

Prior to coronary angiography, 10-mL blood and 10-mL urine samples were taken from all patients. The blood sample was used to measure the uric acid, urea, creatinine, sodium (Na), potassium (K), and bicarbonate levels, while spot urine uric acid and creatinine were measured and spot uric acid to creatinine ratio (UACR) was used to obtain a result similar to that of 24-h urinary uric acid measurement from the urine sample. For additional analyses of NGAL, 10-mL blood and 10-mL urine samples were again obtained from the patients and were centrifuged and preserved at –80 °C. To examine the renal function of patients and to determine whether CIN developed, 10-mL blood and urine samples were taken 48–72 h after coronary angiography and preserved at –80 °C to perform the same tests again. The tests were performed simultaneously in order to avoid any bias due to methodology and calibration differences (Fig. 1). Uric acid levels were analyzed by Cobas 6000 (Roche Modular System) using enzymatic/colorimetric method.

NGAL Analysis through ELISA

For the measurement of NGAL, patients' blood samples were collected into dry tubes and centrifuged immediately (3,500 *g*) for 10 min at +4 °C. Sera were separated in aliquots and frozen immediately at –80 °C. NGAL levels in serum were determined by competitive ELISA using commercial kits (Thermo Fisher, Invitrogen, BMS2202). Intra- and inter-coefficient of variation were 4 and 5.8%, respectively.

Statistical Methods

Means and standard deviations were calculated for continuous variables and counts and percentages for categorical variables. Medians and interquartile ranges were employed for contrast volume and NGAL since they are not normally distributed. CIN was diagnosed if serum creatinine increased by 25% from baseline until 48 h after contrast use. Numerical variables are presented as means (standard deviations) and nominals as percentages. All variables were subjected to Kolmogorov-Smirnov testing to determine whether they were normally distributed. The association of CIN with baseline variables of interest were examined: (1) the χ^2 test and *t* test were used to compare between CIN and non-CIN; (2) a univariate logistic regression model was used to examine the individual baseline variables; and (3) multiple regression with stepwise methods was used to screen the highly potential risk factors. With the stepwise selection, a significance level of 0.3 was required to allow a variable into the model, and a significance level of 0.35 was required for a variable to stay in the model. In addition, since higher NGAL has been considered an important and early biomarker of AKI, we defined 3 risk groups based on the tertiles of the change in NGAL from baseline to 48 h after contrast use (i.e., groups with the change ≤66.3 ng/mL [group 1], ≥79 ng/mL [group 3],

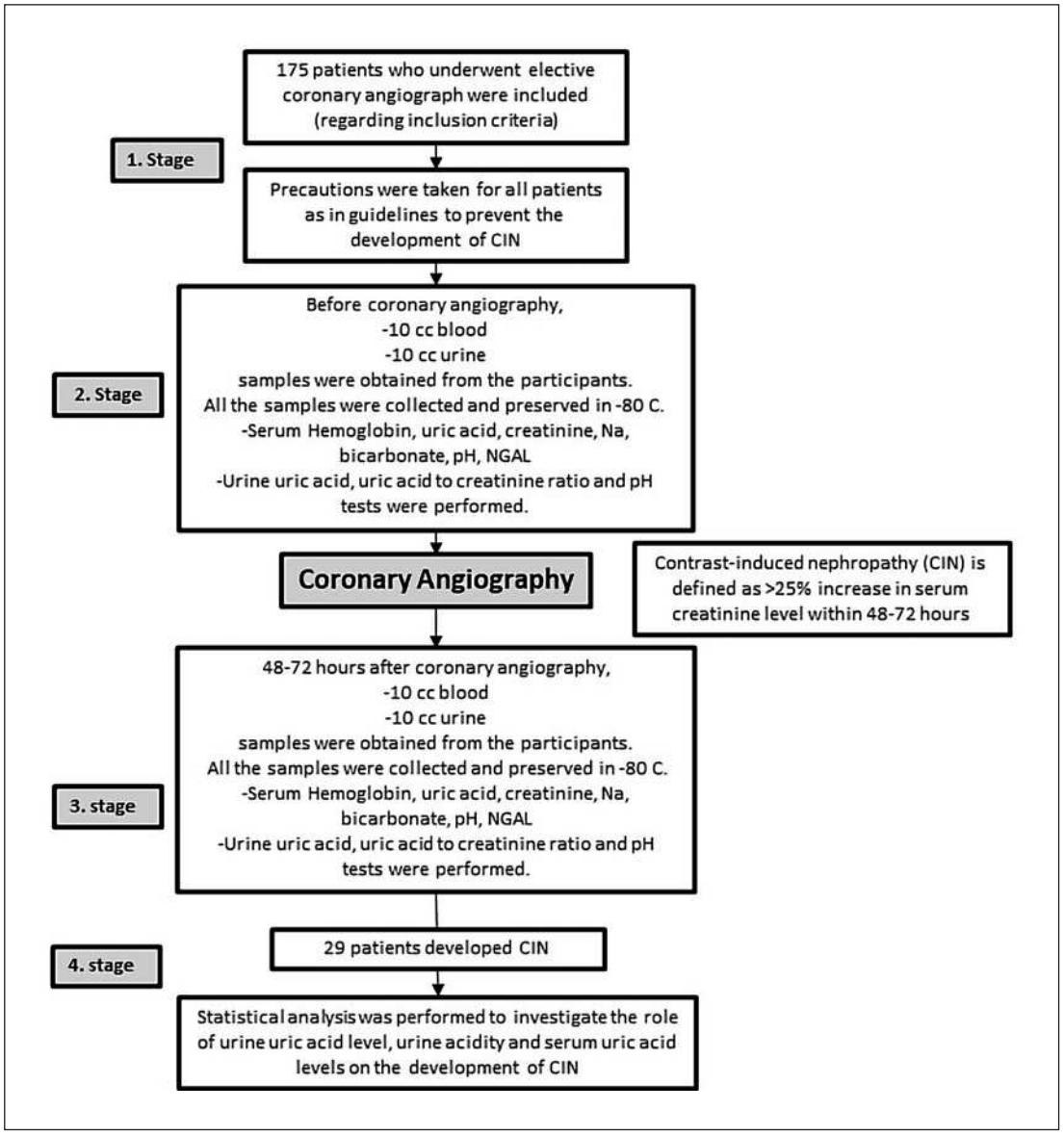

Fig. 1. Flow diagram of the study design.

and between <79 and >66.3 ng/mL [group 2]) and investigated its association with CIN and other baseline variables using the χ^2 test and analysis of variance (ANOVA) in group comparisons. The natural log values of contrast volume and NGAL were used in comparison. The two-sided significance level of 0.05 was used for making a conclusion. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

The mean age of the patients was 67.6 ± 11.2 years and 65.7% were male. Smokers constituted 41.7% of the patients. The percentages of patients with diabetes and hypertension were 35.4 and 70.9%, respectively. Of the 175 subjects included in the final analysis, 29 (16.6%)

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Table 1. Baseline characteristics and comparison between the 2 CIN groups

Baseline variables	Total	CIN (≥25% increased SRC)		*p* value
		no (*n* = 146)	yes (*n* = 29)	
Age, years	67.62 (11.21)	67.06 (11.28)	70.41 (10.58)	0.1417
Male, *n* (%)	115 (65.7)	93 (63.7)	22 (75.9)	0.2075
Diabetes, *n* (%)	62 (35.4)	44 (30.1)	18 (62.1)	0.0010
Hypertension, *n* (%)	124 (70.9)	101 (69.2)	23 (79.3)	0.2728
Smoking, *n* (%)	73 (41.7)	59 (40.4)	14 (48.3)	0.4327
Hemoglobin, g/dL	12.77 (2.18)	12.88 (2.25)	12.26 (1.78)	0.1639
Creatinine, mg/dL	1.11 (0.32)	1.10 (0.30)	1.19 (0.41)	0.2219
eGFR, mL/min/1.73 m^2	65.61 (17.04)	66.53 (16.25)	60.96 (20.21)	0.1074
Serum sodium, mmol/L	141.07 (3.37)	141.39 (3.13)	139.48 (4.08)	0.0227
Serum HCO_3, meq/L	25.88 (2.96)	26.01 (2.90)	25.22 (3.19)	0.1881
Uric acid, mg/dL	6.59 (1.71)	6.56 (1.68)	6.76 (1.85)	0.5728
Serum pH	7.38 (0.04)	7.38 (0.04)	7.38 (0.03)	0.3943
Urine pH	5.83 (0.82)	5.87 (0.84)	5.66 (0.72)	0.1991
UACR	0.47 (0.25)	0.44 (0.22)	0.60 (0.32)	0.0142
Median contrast volume (IQR), mL	135 (80–290)	125 (80–250)	230 (120–335)	0.0358
Median NGAL (IQR), ng/mL	283 (219–420)	275 (215–404)	386 (275–433)	0.0527

Values are means (SD) unless otherwise indicated. The χ^2 test and two-samples *t* test were used to compare the 2 groups if appropriate, and the natural log values of contrast volume and NGAL were used in comparison. CIN, contrast-induced nephropathy; SRC, serum creatinine; SD, standard deviation; eGFR, glomerular filtration rate; HCO_3, bicarbonate; UACR, urine uric acid to creatinine ratio; IQR, interquartile range; NGAL, neutrophil gelatinase-associated lipocalin.

developed CIN defined as an increase by 25% in serum creatinine from baseline to 48 h after contrast use. Table 1 shows the baseline variables with a comparison between the 2 groups. Those who developed CIN had a higher prevalence of diabetes (62.1 vs. 30.1%, $p = 0.001$), lower serum sodium (139 vs. 141 mmol/L, $p = 0.022$), higher UACR (0.60 vs. 0.44, $p = 0.014$), higher contrast volume (230 vs. 125 mL, $p = 0.036$), and higher but non-significant serum NGAL level at baseline (386 vs. 275 ng/mL, $p = 0.053$).

Using univariate analysis of the logistic regression model (Table 2), risk for CIN was observed with diabetes ($p = 0.0016$, odds ratio [OR] = 3.8 [95% CI: 1.7–8.7]), serum sodium ($p = 0.0079$, OR = 0.86 [95% CI: 0.77–0.96]), UACR ($p = 0.0027$, OR = 9.6 [95% CI: 2.2–42.2]), and contrast volume ($p = 0.0385$, OR = 1.8 [95% CI: 1.03–3.09]). Using a multiple logistic regression model with stepwise method of selection, diabetes ($p = 0.0120$, OR = 3.2 [95% CI: 1.3–8.1]) and UACR ($p = 0.0163$, OR = 6.9 [95% CI: 1.4–33.4]) were the 2 risk factors finally identified.

Urine NGAL values (as a more sensitive marker of AKI) from baseline to 48 h can be found in Tables 3 and 4. As shown in Tables 3 and 4, age, hemoglobin level, creatinine level, glomerular filtration rate, serum sodium level, serum bicarbonate, serum uric acid, and urine UACR were significantly different between the different tertiles of urinary NGAL. Patients in the higher NGAL tertile had a higher baseline serum uric acid and urine UACR compared to the other 2 groups.

Discussion

In this study, we investigated the role of urine uric acid levels, urine pH, serum bicarbonate, and serum uric acid levels in the development of CIN in patients undergoing coronary angiography. We found that diabetes mellitus, high dose of contrast medium, and high urine

Table 2. Results from univariate and multiple logistic regression models

Baseline variables	Univariate analysis		Variables which stayed in the final model with stepwise selection	
	p value	HR (95% CI)	*p* value	HR (95% CI)
Age	0.1429	1.028 (0.991, 1.067)		
Male	0.2119	1.791 (0.717, 4.472)	0.1245	2.270 (0.798, 6.461)
Diabetes	0.0016	3.793 (1.655, 8.693)	0.0120	3.228 (1.294, 8.054)
Hypertension	0.2768	1.708 (0.651, 4.482)		
Smoking	0.4338	1.376 (0.619, 3.063)		
Hemoglobin	0.1647	0.877 (0.729, 1.055)		
Creatinine	0.1304	2.395 (0.772, 7.429)		
eGFR	0.1096	0.982 (0.959, 1.004)		
Serum sodium	0.0079	0.857 (0.765, 0.960)	0.1242	0.906 (0.800, 1.027)
Serum HCO_3	0.1884	0.911 (0.793, 1.047)		
Uric acid	0.5706	1.070 (0.848, 1.349)		
Serum pH	0.3927	0.015 (<0.001, 221.988)		
Urine pH	0.2007	0.705 (0.412, 1.205)		
UACR	0.0027	9.614 (2.189, 42.228)	0.0163	6.901 (1.427, 33.373)
Contrast volume	0.0385	1.785 (1.031, 3.089)	0.1377	1.579 (0.864, 2.888)
NGAL	0.0530	2.530 (0.988, 6.478)	0.1450	2.204 (0.762, 6.382)

The natural log values of contrast volume and NGAL were used in the analysis. eGFR, glomerular filtration rate; HCO_3, bicarbonate; UACR, urine uric acid to creatinine ratio; NGAL, neutrophil gelatinase-associated lipocalin.

Table 3. Baseline characteristics and comparison between the 3 groups of NGAL change

Variables	Groups based on change in NGAL			*p* value
	≤66.3 ng/mL	between <79 and >66.3 ng/mL	≥79 ng/mL	
Age, years	63.80 (10.44)	70.26 (11.21)	68.92 (10.95)	0.0037
Male, *n* (%)	40 (67.8)	37 (63.8)	39 (65.0)	0.8962
Diabetes, *n* (%)	15 (25.4)	20 (34.5)	28 (46.7)	0.0523
Hypertension, *n* (%)	37 (62.7)	44 (75.9)	45 (75.0)	0.2113
Smoking, *n* (%)	24 (40.7)	26 (44.8)	24 (40.0)	0.8483
Hemoglobin, g/L	13.49 (1.85)	12.72 (2.30)	12.12 (2.17)	0.0025
Creatinine, mg/dL	1.03 (0.20)	1.08 (0.32)	1.22 (0.37)	0.0024
eGFR, mL/min/1.73 m^2	71.61 (12.57)	67.24 (17.71)	58.24 (17.53)	<0.0001
Serum sodium, mmol/L	142.42 (2.31)	140.69 (2.90)	140.22 (4.20)	0.0007
Serum HCO_3, meq/L	26.35 (2.96)	26.17 (3.16)	25.11 (2.58)	0.0435
Uric acid, mg/dL	6.49 (1.57)	6.15 (1.49)	7.10 (1.89)	0.0084
Serum pH	7.38 (0.04)	7.38 (0.03)	7.38 (0.05)	0.8361
Urine pH	5.79 (0.87)	5.98 (0.80)	5.73 (0.78)	0.2243
UACR	0.36 (0.15)	0.47 (0.25)	0.57 (0.27)	<0.0001
Median contrast volume (IQR), mL	4.86 (3.91, 6.41)	5.04 (3.55, 6.35)	4.92 (3.22, 6.40)	0.8244

Values are means (SD) unless otherwise indicated. The χ^2 test and analysis of variance (ANOVA) were used if appropriate. The natural log value of contrast volume was used in comparison. NGAL, neutrophil gelatinase-associated lipocalin; eGFR, glomerular filtration rate; HCO_3, bicarbonate; UACR, urine uric acid to creatinine ratio; IQR, interquartile range; SD, standard deviation.

Kidney Blood Press Res 2020;45:131–141
DOI: 10.1159/000504547
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Table 4. Paired comparisons with the Tukey method after ANOVA as shown in Table 3

Dependent variables	Comparison[a]		Difference (95% CI)
Age	3: ≥79	–1: ≤66.3	5.12 (0.41, 9.83)
	1: ≤66.3	–2: between	–6.46 (–11.21, –1.71)
Hemoglobin	3: ≥79	–1: ≤66.3	–1.37 (–2.29, –0.45)
Creatinine	3: ≥79	–2: between	0.14 (0.01, 0.27)
	3: ≥79	–1: ≤66.3	0.19 (0.06, 0.33)
eGFR	3: ≥79	–1: ≤66.3	–13.37 (–20.35, –6.39)
	3: ≥79	–2: between	–9.00 (–16.01, –1.98)
Serum sodium	1: ≤66.3	–2: between	1.73 (0.32, 3.15)
	3: ≥79	–1: ≤66.3	–2.21 (–3.61, –0.80)
Serum uric acid	3: ≥79	–2: between	0.95 (0.22, 1.67)
UACR	3: ≥79	–2: between	0.10 (0.00, 0.20)
	3: ≥79	–1: ≤66.3	0.21 (0.11, 0.31)
	1: ≤66.3	–2: between	–0.11 (–0.21, –0.01)

Only the comparisons with a significant difference based on type I error = 0.05 were included. eGFR, estimated glomerular filtration rate; UACR, urine uric acid to creatinine ratio. [a] Numbers 1–3 indicate tertile groups based on NGAL (ng/mL).

UACR levels were independent risk factors for the development of CIN, while serum bicarbonate levels, serum uric acid, and urine pH were not significant risk factors.

CIN is thought to be becoming less frequent [7]. Nevertheless, in our study, 16.6% of the patients (29 out of 175) developed CIN, and similar frequencies (10–20%) have been reported by others [20, 21]. CIN can result in permanent kidney damage even if renal function initially returns to normal, and the mortality risk significantly increases in high-risk patients [21]. Indeed, CIN increases short- and long-term mortality risk 2–4 times, especially in patients at high risk [22]. Therefore, identification of risk factors for CIN is important in terms of the reduction of the related complications.

Known risk factors for CIN include older age, chronic renal insufficiency, diabetes mellitus, advanced cardiovascular disease, hypotension, anemia, and high dose of contrast medium [23]. More recently, hyperuricemia has also been identified as a risk factor [1]. We identified high NGAL levels in patients with CIN. In a previous meta-analysis, Tong et al. [24] reported that increased serum and urine NGAL levels seem to be useful biomarkers in the early prediction of CIN. Additionally, high urine UACR levels were determined as an independent risk factor for the development of CIN. The identification of a high baseline urine UACR level as an independent risk factor is novel and may be relevant to the potential of radiocontrast to acutely increase urine uric acid, potentially leading to urinary crystal formation and tubular injury. Of note, diabetes is also known to cause uricosuria [25], and it is commonly identified as a risk factor for CIN, including in this study. These findings suggest that baseline urine UACR precedes and predicts acute changes in renal function and would also be consistent with uricosuria as a potential mechanism for kidney injury.

The contribution of urine acidity is known to increase the toxicity of uric acid and other toxins by increasing the chelation of urine uric acids in the tubules and renal medulla [19]. The damage of CIN occurs with a similar mechanism in tubules and medulla; however, the relationship between urine pH and the risk of CIN has not yet been studied. Although urine pH of the patients who developed CIN was lower than in the control group in our study, the

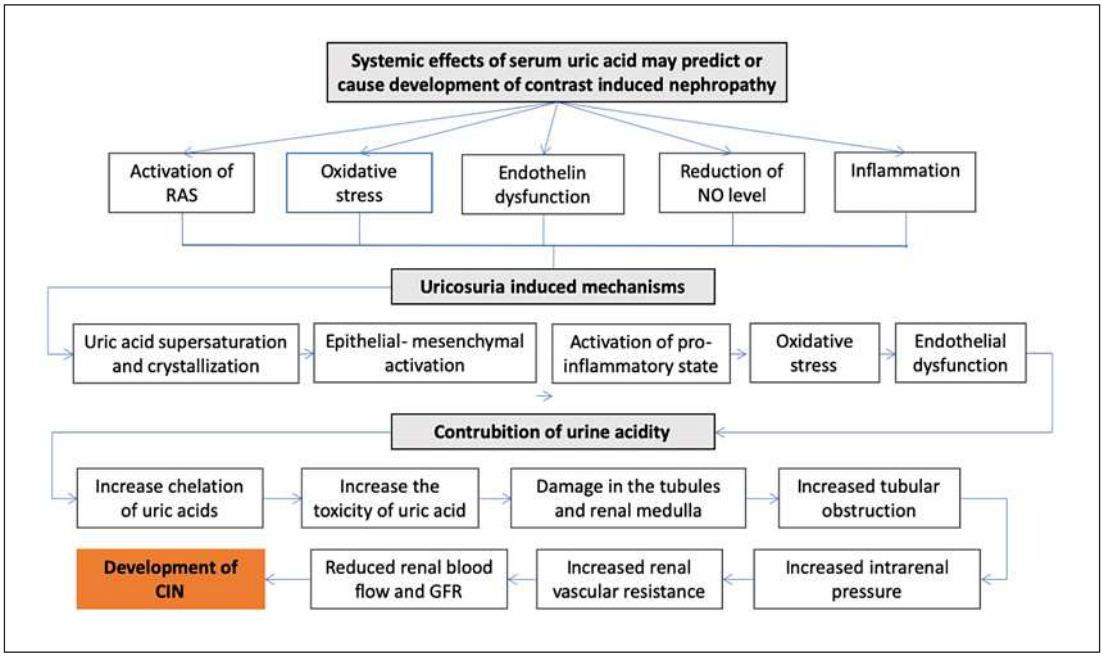

Fig. 2. Postulated mechanisms for the effect of uric acid on the development of contrast-induced nephropathy (CIN).

difference was not statistically significant. This information supports the role of urine acidity on influencing the risk for AKI in CIN, but there is a need for a larger prospective study to identify urine pH as a risk factor.

Recently, high serum uric acid has also been reported to be an independent predictor for CIN in some studies [11, 26–28]. Mendi et al. [1] evaluated serum uric acid as a potential risk factor for CIN in 450 patients undergoing percutaneous coronary intervention and found a serum uric acid level of >5.4 mg/dL as a predictor for the development of CIN (sensitivity of 70%, specificity of 67%). In another study, Barbieri et al. [28] found that elevated serum uric acid (>7 mg/dL) was associated with the development of CIN in patients undergoing coronary angiography or percutaneous coronary intervention (adjusted OR = 1.42 [95% CI: 1.04–1.93], p = 026). Conversely, other studies failed to demonstrate a relationship between uric acid and CIN [29, 30]. In the current study, patients with AKI tended to have higher baseline serum uric acid levels, and lower serum bicarbonate levels and urine pH; however, they were not statistically different from the subjects not developing AKI.

From a therapeutic perspective, 2 prophylaxis trials have reported that allopurinol can prevent contrast nephropathy [31, 32], and a recent analysis suggested that it is the most effective of all agents tried to date [33]. In contrast, Iranirad et al. [34] could not show any additional benefit of allopurinol compared to hydration for the development of CIN in high-risk patients. Likewise, another study comparing N-acetylcysteine with allopurinol also found no significant difference in the effectiveness of these medications to prevent CIN [35].

Nevertheless, despite ongoing controversy around the effectiveness of lowering plasma uric acid pharmacologically, elevated urine uric acid levels may predispose to the development of urate crystals, leading to inflammation-related tubular injury, especially in acidic urine [36, 37]. An increase in urine uric acid levels may also induce tubular injury through epithelial-mesenchymal transformation [38], endothelial dysfunction, oxidative stress, and elevations in C-reactive protein [39–42]. Thus, these mechanisms may in part explain why

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DOI: 10.1159/000504547
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higher urine UACR levels were present in the patients who developed CIN in our study. Figure 2 shows the potential role of urine uric acid level and urine acidity in the pathogenesis of CIN.

In terms of limitations, the selected patients were from a single center, which, hence, may limit generalizability. The sample size was also relatively small, and we did not follow up patients in the long term. Lastly, the current study did not investigate the association between higher urine UACR and short- and long-term prognostic value, such as new cardiovascular event, mortality, and hospitalization.

In conclusion, a higher urine UACR is associated with the development of CIN in patients undergoing elective coronary angiography. Further studies are warranted to elucidate underlying mechanisms as well as randomized controlled trials with a large sample size to determine whether lowering serum uric acid and the baseline urine UACR can reduce the development of CIN.

Acknowledgements

M.K. gratefully acknowledges the use of the services and facilities of the Koc University Research Center for Translational Medicine (KUTTAM), funded by the Presidency of Turkey, Presidency of Strategy and Budget. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Presidency of Strategy and Budget.

Statement of Ethics

Koc University School of Medicine ethics committee approved the study protocol. Written informed consent was obtained from all subjects before enrollment.

Disclosure Statement

All authors declare that they have no conflicts of interest.

Funding Sources

This study was not funded by any grant.

Author Contributions

Concept: G.A., M.K.; Supervision: G.A., M.K.; Materials: G.A., V.C.; Data: G.A., N.E., S.Y., V.C.; Analysis: G.A., Z.Y., M.L.G., D.Z.I.C., S.I.; Writing: G.A., M.K., D.S., B.A.

Critical revision: G.A., M.K., B.A., A.A.S., M.L.G, D.S., R.J.J., A.C.

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Kidney Blood Press Res 2020;45:131–141
DOI: 10.1159/000504547
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