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DNA Damage Analysis with Oxidative Stress Index and 8-Hydroxy 2'-Deoxy Guanosine Level in Patients Developing Contrast Nephropathy After Coronary Angiography

ABSTRACT

Background: Contrast-induced nephropathy (CIN) is a common cause of hospital-acquired acute kidney injury, and oxidative stress is thought to play a crucial role in its pathogenesis. Evidence regarding DNA damage after contrast exposure remains limited. This study aimed to evaluate oxidative stress and DNA damage in patients developing CIN by assessing total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), and 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels as well as clinical factors associated with CIN.

Methods: A total of 191 patients undergoing coronary angiography were prospectively evaluated. Blood samples were obtained before the procedure and at 72 hours afterward. CIN was defined as ≥25% or ≥0.5 mg/dL increase in serum creatinine. Patients were classified into CIN (n = 85) and control groups (n = 106).

Results: Advanced age and heart failure were the strongest predictors of CIN. Hypertension, anemia, chronic kidney disease, and hyperuricemia were also more frequent in the CIN group. After angiography, TAS increased and TOS decreased in both groups; however, the reduction in TOS reached significance only in controls. Post-procedure TAS levels were higher in the CIN group ($P = .033$). Baseline 8-OHdG levels were higher in patients who later developed CIN, whereas the post-procedure decline in 8-OHdG was significant only in controls ($P = .02$). No significant differences in TOS, OSI, or post-procedure 8-OHdG were observed between groups.

Conclusion: This study is among the first to investigate DNA damage in CIN using 8-OHdG levels. The higher baseline DNA damage in CIN patients and the greater reduction in controls suggest a possible link between DNA injury and CIN. Oxidative stress markers did not differ significantly, which may reflect the use of modern low-toxicity contrast agents or the involvement of multifactorial mechanisms. Further studies are needed to clarify the role of oxidative stress and DNA damage in CIN.

Keywords: Contrast-induced nephropathy, DNA damage, OSI, oxidative stress, 8-OHdG

INTRODUCTION

Contrast-induced nephropathy (CIN) is a common and preventable iatrogenic acute kidney injury that develops as a result of the use of contrast agents in radiological imaging and interventional procedures. It is the third most frequent cause of hospital-acquired acute kidney injury.[1] The most widely accepted definition of CIN is an increase in serum creatinine by ≥25% or an absolute increase of ≥0.5 mg/dL within 48-72 hours after exposure to contrast media.[2] Although the term "contrast-associated acute kidney injury (CA-AKI)" has been increasingly adopted in recent literature, the term "contrast-induced nephropathy (CIN)" is used in the present study to maintain consistency with the diagnostic criteria applied at the time of study design and with previously published studies. Terminological consistency is preserved throughout the manuscript.

Risk factors for CIN include heart failure (HF), diabetes mellitus (DM), chronic kidney disease (CKD), advanced age (>70 years), dehydration, anemia, and high

ORIGINAL INVESTIGATION

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volumes of contrast administration.[3] The impact of these factors on CIN may be related to the patient's physiological reserve and antioxidant capacity.

Oxidative stress develops as a result of an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense mechanisms. Under normal physiological conditions, ROS are eliminated by antioxidant systems; however, when this balance is disrupted, cellular damage occurs at the level of lipid peroxidation, protein oxidation, and DNA injury.[4]

Total antioxidant status (TAS) reflects the cumulative effect of all antioxidants present in serum, whereas total oxidant status (TOS) indicates the overall level of oxidant molecules. The ratio of these 2 parameters is defined as the oxidative stress index (OSI), which provides a reliable measure of the oxidant–antioxidant balance in the body.[5] Previous studies have reported increased oxidative stress in patients who developed CIN, while others have not demonstrated significant changes in OSI levels.[6]

8-hydroxy-2′-deoxyguanosine (8-OHdG) is considered one of the most sensitive biomarkers of oxidative DNA damage.[4] Among many oxidative stress markers, 8-OHdG is notable because it is directly linked to oxidative DNA damage.[7] However, studies evaluating the association between CIN and 8-OHdG are scarce. Experimental models have shown elevated 8-OHdG levels following contrast exposure, whereas human studies have yielded inconsistent results.[8] Therefore, this study aimed to investigate TAS, TOS, OSI, and 8-OHdG levels to clarify the potential relationship between CIN, oxidative stress, and DNA damage.

METHODS

This prospective observational comparative study was conducted among patients who underwent coronary angiography (CAG) at Eskişehir Osmangazi University Hospital between February 2021 and April 2022. The study was designed to compare oxidative stress and DNA damage markers between patients who developed contrast-induced nephropathy (CIN) and those who did not develop CIN; it was not designed to estimate the incidence of CIN in the overall population who underwent CAG. The study was approved by the Ethics Committee for Clinical Research of Eskişehir Osmangazi University (Decision no: 41, dated February 4, 2021) and was supported by the Eskişehir Osmangazi University Scientific Research Projects (BAP) under project number 1621. Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

Because paired baseline and 72-hour post-procedural biochemical measurements were not routinely available for all patients undergoing CAG, eligible participants were identified among patients with accessible biochemical data at both time points. A pre-study sample size calculation indicated that a minimum of 82 patients with CIN and 106 controls without CIN were required. Recruitment of the control group was stopped after the planned number of 106 patients of the non-CIN group had been reached, whereas eligible patients who developed CIN continued to be included until the target sample size was achieved. The final study sample, therefore, consisted of 85 patients with CIN and 106 controls without CIN.

Blood samples were collected before CAG and at 72 hours after the procedure to assess oxidative stress parameters and renal function tests. Patients who met the criteria for contrast-induced nephropathy (CIN) at 72 hours were classified as the case group (n=85), whereas those without a significant increase in serum creatinine compared with baseline were classified as the control group (n=106). Since CIN typically manifests on the second day following contrast exposure, and delayed cases may also present with elevated creatinine at 72 hours, all assessments were performed at this time point. The total volume of contrast administered during coronary angiography was recorded for each patient. All patients received iobitridol, a water-soluble, non-ionic, monomeric, low-osmolar iodine-based contrast agent during CAG.

Peri-procedural management, including hydration and preventive strategies for CIN, was planned by the cardiology team based on individual clinical assessment and institutional practice. However, preventive measures were not applied according to a predefined standardized study protocol for all patients; instead, they were individualized according to renal function, volume status, comorbidities, cardiovascular risk profile, and the risk of fluid overload.

In patients who received prophylaxis, intravenous hydration was generally initiated approximately 12 hours before the procedure and continued for approximately 12 hours after the procedure. For this purpose, isotonic saline or, in selected patients, sodium bicarbonate-based intravenous hydration was used, with the hydration rate commonly adjusted to 1-1.5 mL/kg/hr. Additional preventive approaches included oral N-acetylcysteine, statin therapy, or combinations of these strategies. When used, N-acetylcysteine was administered orally at a dose of 1200 mg before the procedure and 1200 mg after the procedure. Statin prophylaxis was arranged according to the patient's current statin use and

HIGHLIGHTS

- Advanced age and heart failure were identified as the most prominent clinical predictors of contrast-induced nephropathy (CIN).
- Total antioxidant status (TAS) increased after coronary angiography in both groups, with higher postprocedural TAS levels observed in patients who developed CIN.
- Oxidative stress markers (TOS and OSI) decreased after the procedure, with a more pronounced reduction in TOS observed in the non-CIN control group.
- A significant post-procedural decrease in 8-OHdG levels was detected only in the control group, suggesting a differential DNA damage response in CIN.
- This study provides human evidence evaluating oxidative stress and oxidative DNA damage simultaneously in the context of CIN.

cardiovascular risk profile, based on the cardiology team's assessment. Nephrology consultation was requested only when clinically indicated, and no routine nephrology-directed intervention was applied.

Inclusion criteria: Patients aged ≥18 years who had an indication for coronary angiography and available biochemical evaluations performed before and after the procedure**.**

Exclusion criteria: Active malignancy, use of nephrotoxic drugs, sepsis, hypotension, prior radiotherapy/chemotherapy, advanced CKD requiring renal replacement therapy, and overt ischemic acute kidney injury.

Laboratory Analyses

For TAS, TOS, and 8-OHdG assays, blood samples were centrifuged at 1500 rpm and plasma was stored at −80°C until analysis.

- **Measurement of Total Antioxidant Status (TAS):** Serum TAS levels were determined using a commercial kit (Reference no: RL0017, Rel Assay, Gaziantep, Türkiye). The test is based on the reduction of the colored radical cation 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid; ABTS• +) to its colorless form by antioxidants, with absorbance measured spectrophotometrically.[9] Results were expressed as mmol H_2O_2 equiv/L.
- **Measurement of Total Oxidant Status (TOS):** Serum TOS levels were measured with a commercial kit (Reference no: RL0024, Rel Assay, Gaziantep, Türkiye). The method is based on the oxidation of ferrous ion to ferric ion by oxidants present in the sample, forming a colored complex with xylenol orange under acidic conditions. The color intensity , measured spectrophotometrically, is directly proportional to the total amount of oxidant molecules. Results were expressed as mmol H_2O_2 equiv/L.[10]
- **Calculation of Oxidative Stress Index (OSI):**
- OSI (arbitrary units) = (TOS [μmol H_2O_2 equiv/L] / TAS [mmol H_2O_2 equiv/L]) × 100.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range, [IQR]), as appropriate. As most continuous variables did not meet the assumptions of a normal distribution, comparisons between two independent groups were performed using the Mann–Whitney *U*-test. Comparisons of paired pre- and post-procedural measurements were performed using the Wilcoxon signed-rank test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Correlations were assessed using Spearman's correlation analysis. A 2-sided *P*-value < .05 was considered statistically significant.

For multivariable logistic regression analysis, serum uric acid level, age, hypertension, heart failure stage, chronic kidney disease stage, and baseline hemoglobin level were initially entered into the model. A backward stepwise elimination procedure based on the Wald statistic was then applied to obtain the final multivariable model. Variables with the weakest contribution were sequentially removed, and the model was re-estimated at each step. Regression results were reported as regression coefficient (B), standard error (SE[B]), odds ratio (Exp[B]), 95% confidence interval (CI), and *P*-value.

RESULTS

A total of 191 patients were included in the study and were divided into 2 groups: those who developed contrast-induced nephropathy (CIN) (n = 85, 44.5%) and those who did not (n = 106, 55.5%). No significant difference was observed between the groups with respect to sex distribution (CIN group: 45.9% female, 54.1% male; control group: 39.6% female, 60.4% male; *P* = .384). However, the mean age of patients who developed CIN (68.13 ± 10.37 years) was significantly higher compared with the control group (61.03 ± 9.97 years; *P* < .001).

Comorbidities such as hypertension (HT), congestive heart failure (CHF), and chronic kidney disease (CKD) were more frequent in the CIN group compared with controls. The prevalence of HT was 72.9% in the CIN group versus 57.5% in the control group (*P* = .027). Congestive heart failure (CHF) was also more common among CIN patients, with stage 3 CHF present in 20% of the CIN group compared with only 2.8% in the control group (*P* < .001). Similarly, the prevalence of stage 3 CKD was significantly higher in the CIN group (29.4%) than in the control group (4.7%) (*P* < .001). The baseline characteristics of the case and control groups are presented in Table 1.

In the final multivariable logistic regression model, age (OR = 1.054, *P* = .004, 95% CI: 1.017-1.092) and heart failure stage (overall *P* < .001) were retained. Compared with patients without heart failure, heart failure stage 1 was significantly associated with the outcome (OR = 0.069, *P* = .001, 95% CI: 0.015-0.329), whereas heart failure stage 2 (OR = 0.235, *P* = .084, 95% CI: 0.045-1.213) and stage 3 (OR = 0.275, *P* = .157, 95% CI: 0.046-1.643) were not statistically significant (Table 2).

In the CIN group, baseline hemoglobin (Hb: 12.86 ± 2.08 g/dL) and hematocrit (Hct: 38.75 ± 5.72%) levels were significantly lower than those in the control group (*P* = .010 and *P* = .010, respectively) (Table 3). Serum uric acid levels were significantly higher in the CIN group (6.20 vs. 5.40 mg/dL; *P* < .001). No significant difference was observed between the groups with respect to body mass index (BMI) (Table 3).

When prophylactic strategies were evaluated according to CIN status, a variety of approaches, including intravenous hydration, N-acetylcysteine, sodium bicarbonate–based intravenous hydration, and statins, were observed to be used in both groups. The proportion of patients who did not receive any prophylaxis was 31.8% in the group that developed nephropathy and 56.6% in the group that did not develop nephropathy. In contrast, combination therapies involving multiple agents were more frequently used in patients who developed nephropathy. Statin use was similar between the two groups (22.4% vs. 25.5%). The median contrast volume administered during coronary angiography

Table 1. Baseline Characteristics of Patients with and Without Contrast-Induced Nephropathy

Variables	CIN (+) (n = 85)	CIN (−) (n = 106)	*P* value
Sex, n (%)			.384
Female	39 (45.9)	42 (39.6)	
Male	46 (54.1)	64 (60.4)	
Age, years (mean ± SD)	68.13 ± 10.37	61.03 ± 9.97	<.001
DM, n (%)	43 (50.6)	47 (44.3)	.390
HT, n (%)	62 (72.9)	61 (57.5)	.027
HPL, n (%)	37 (43.5)	50 (47.2)	.616
Congestive heart failure, n (%)			<.001
None	30 (35.3)	75 (70.8)	
Stage 1	24 (28.2)	20 (18.9)	
Stage 2	14 (16.5)	8 (7.5)	
Stage 3	17 (20.0)	3 (2.8)	
CKD, n (%)			<.001
None	24 (28.2)	59 (55.7)	
Stage 1	13 (15.3)	22 (20.8)	
Stage 2	18 (21.2)	19 (17.9)	
Stage 3	25 (29.4)	5 (4.7)	
Stage 4	5 (5.9)	1 (0.9)	

CKD, chronic kidney disease; CIN, contrast-induced nephropathy; DM, diabetes mellitus; HPL, hyperlipidemia; HT, hypertension.

was 110 mL (IQR, 80-170) in the CIN group and 100 mL (IQR, 80-150) in the non-CIN group, with no statistically significant difference between the groups ($P = .079$).

Table 2. Logistic Regression Analysis of Predictors of Contrast-Induced Nephropathy

Variables	B	SE β	OR (Exp β)	95% CI	*P* value
Age	0.052	0.018	1.054	1.017-1.092	.004
Heart failure*					<.001
Stage 1	−2.671	0.796	0.069	0.015-0.329	.001
Stage 2	−1.449	0.838	0.235	0.045-1.213	.084
Stage 3	−1.291	0.912	0.275	0.046-1.643	.157

B, regression coefficient; CI, confidence interval; OR, odds ratio; SE, standard error.
*Heart failure stages were entered into the model as categorical variables, with "no heart failure" used as the reference category. Odds ratios for heart failure stages represent relative odds compared with patients without heart failure.

With respect to oxidative stress parameters, post-CAG TAS levels were significantly higher in the CIN group compared with controls (1.75 vs. 1.67 mmol H_2O_2 equiv/L; $P = .033$). No significant differences were observed between the groups in terms of TOS, OSI, or 8-OHdG levels (Table 3).

A positive correlation was observed between TAS levels and both age ($r = 0.173$, $P = .017$) and serum uric acid levels ($r = 0.609$, $P < .001$).

Comparisons of pre- and post-CAG changes in oxidative stress and DNA damage markers are as follows:

Pre- and post-CAG changes in TAS, TOS, OSI, and 8-OHdG levels were compared separately between patients with and without CIN. In both groups, TAS levels increased after CAG; however, no statistically significant difference was observed

Table 3. Comparison of Laboratory Parameters Between Contrast-Induced Nephropathy and Non–Contrast-Induced Nephropathy Groups

Parameters	CIN (+)	CIN (−)	P value
BMI (kg/m^2) (mean ± SD)	27.01 ± 3.99	28.48 ± 5.50	.071
Hemoglobin (g/dL) (mean ± SD)	12.86 ± 2.08	13.86 ± 1.93	.010
Hematocrit (%) (mean ± SD)	38.75 ± 5.72	41.56 ± 5.21	.010
Variables	**CIN (+) Median [IQR]**	**CIN (−) Median [IQR]**	**P value**
Uric acid (mg/dL)	6.20 (4.70-7.32)	5.40 (4.50-6.20)	<.001
BUN (mg/dL) pre-CAG	18.80 (14.95-24.70)	14.65 (12.37-17.42)	<.001
BUN (mg/dL) post-CAG	25.80 (19.15-37.90)	14.75 (12.47-19.22)	<.001
Creatinine (mg/dL) pre-CAG	0.95 (0.81-1.26)	0.88 (0.72-1.01)	.040
Creatinine (mg/dL) post-CAG	1.27 (1.06-1.75)	0.83 (0.73-1.01)	<.001
eGFR (mL/min/1.73 m^2) pre-CAG	65.00 (51.50-89.50)	85.00 (69.15-90.00)	<.001
eGFR (mL/min/1.73 m^2) post-CAG	50.00 (31.50-68.00)	85.00 (72.75-90.00)	<.001
TAS (mmol H_2O_2 equiv/L) pre-CAG	1.63 (1.47-1.84)	1.61 (1.42-1.76)	.142
TAS (mmol H_2O_2 equiv/L) post-CAG	1.75 (1.58-2.00)	1.67 (1.51-1.84)	.033
TOS (μmol H_2O_2 equiv/L) pre-CAG	4.81 (3.23-10.30)	5.72 (1.67-9.87)	.448
TOS (μmol H_2O_2 equiv/L) post-CAG	4.13 (3.26-5.87)	3.55 (2.74-4.75)	.060
OSI (arbitrary units) pre-CAG	3.18 (1.94-6.83)	3.50 (2.28-6.61)	.332
OSI (arbitrary units) post-CAG	2.44 (1.83-3.58)	2.12 (1.67-2.76)	.075
8-OHdG (ng/mL) pre-CAG	11.20 (8.85-12.79)	11.09 (9.53-14.30)	.037
8-OHdG (ng/mL) post-CAG	10.37 (8.15-13.23)	10.26 (8.51-13.09)	.837

BMI, body mass index; BUN, blood urea nitrogen; CAG, coronary angiography; CIN, contrast-induced nephropathy; GFR, glomerular filtration rate; OSI, oxidative stress index; TAS, total antioxidant status; TOS, total oxidant status; 8-OhDG, 8-hydroxy-2′-deoxyguanosine.

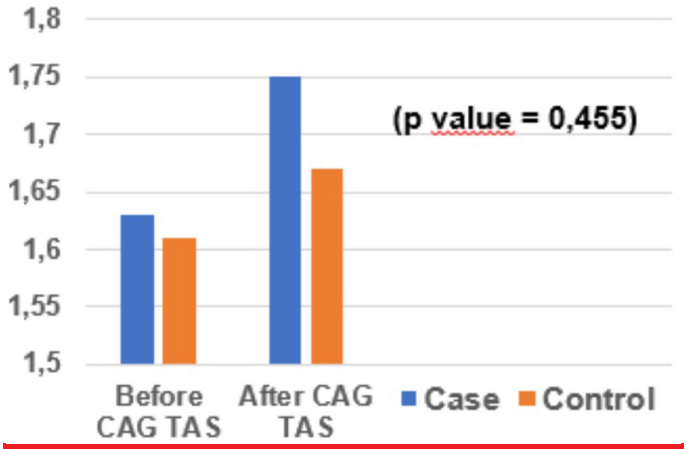

Figure 1. Comparison of total antioxidant status before and after coronary angiography in patients with and without contrast-induced nephropathy. CAG, coronary angiography; TAS, total antioxidant status.

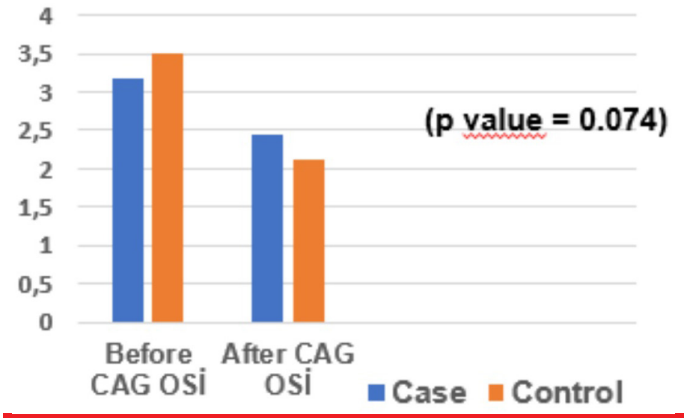

Figure 3. Comparison of oxidative stress index before and after coronary angiography in patients with and without contrast-induced nephropathy. CAG, coronary angiography; OSI, oxidative stress index.

between the groups ($P = .455$) (Figure 1). TOS levels decreased in both groups, but the reduction was more pronounced in the control group ($P = .046$) (Figure 2). OSI levels decreased after CAG in both groups, with no significant intergroup difference (Figure 3). In contrast, post-CAG 8-OHdG levels showed a greater decrease in the control group compared with the CIN group ($P = .020$) (Figure 4).

In both patients who underwent percutaneous intervention and those who did not, a significant increase in TAS levels was observed after CAG ($P = .002$ and $P = .003$, respectively), while TOS ($P = .031$ and $P < .001$) and OSI ($P = .009$ and $P < .001$) levels significantly decreased. However, no statistically significant differences in oxidative stress parameters were detected between the 2 groups (Table 4).

DISCUSSION

In this study, similar to previous reports, advanced age and heart failure were identified as the strongest predictors of CIN. In addition, it was observed that CKD, anemia, hypertension, and hyperuricemia were also important factors associated with CIN development. Previous studies have suggested that female sex may confer a higher risk of CIN, which has been attributed to sex-related differences in pharmacokinetics, plasma protein binding rates, and organ functions.[11,12] However, in the cohort, no significant association was found between sex and the occurrence of CIN. The risk score developed by Mehran et al[13] included age >75 years, congestive heart failure, hypertension, diabetes mellitus, CKD (GFR < 60 mL/min), anemia, the amount of contrast media used, and hypotension as the major risk factors for CIN. In line with these findings, this study demonstrated that CIN was more frequently observed in patients with congestive heart failure, chronic kidney disease, advanced age, and lower hemoglobin levels, thereby supporting previous evidence. Reduced left ventricular systolic function may predispose patients to contrast-related renal injury by decreasing cardiac output and, consequently, impairing effective renal perfusion. Contemporary heart failure studies have

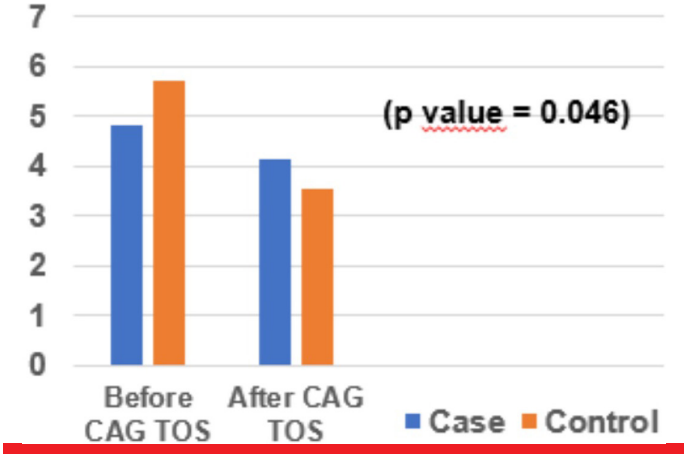

Figure 2. Comparison of total oxidant status before and after coronary angiography in patients with and without contrast-induced nephropathy. CAG, coronary angiography; TOS, total oxidant status.

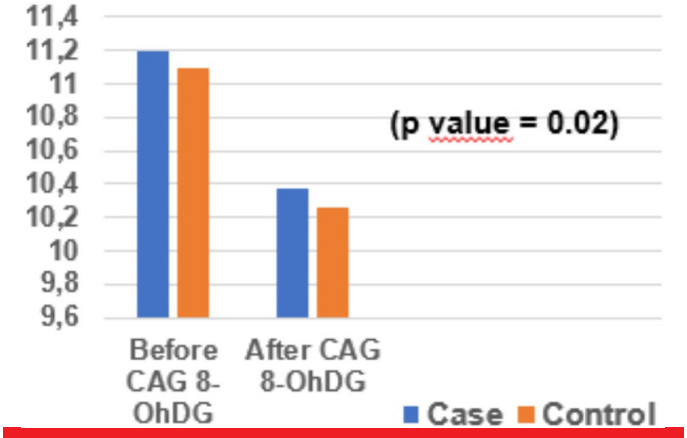

Figure 4. Comparison of 8-hydroxy-2′-deoxyguanosine levels before and after coronary angiography in patients with and without contrast-induced nephropathy. 8-OHdG, 8-Hydroxy-2′-deoxyguanosine; CAG, coronary angiography.

Table 4. Comparison of Oxidative Stress Parameters Before and After Coronary Angiography in Patients with and Without Percutaneous Coronary Intervention

Variables	Before CAG (No PCI)	After CAG (No PCI)	*P*-value (No PCI)	Before CAG (PCI)	After CAG (PCI)	*P*-value (PCI)
TAS	1.61 (1.43-1.80)	1.70 (1.49-1.85)	.003	1.63 (1.47-1.83)	1.78 (1.58-1.97)	.002
TOS	5.25 (3.39-9.77)	3.72 (2.90-4.87)	<.001	5.59 (3.48-911.10)	4.01 (3.11-5.73)	.031
OSI	3.30 (2.11-6.67)	2.18 (1.69-2.85)	<.001	3.46 (2.00-6.41)	2.41 (1.70-3.60)	.009
8-OHdG	10.96 (9.51-14.19)	10.28 (8.22-13.86)	.003	11.26 (8.96-12.84)	10.19 (8.70-12.53)	.055

CAG, coronary angiography; OSI, oxidative stress index; PCI, percutaneous coronary intervention; TAS, total antioxidant status; TOS, total oxidant status; 8-OHdG, 8-hydroxy-2′-deoxyguanosine.

emphasized the prognostic impact of cardiac dysfunction and systemic hemodynamic compromise. Consistent with the literature, a higher incidence of contrast-induced nephropathy has been reported in patients with a left ventricular ejection fraction <50%. The findings are in accordance with this pathophysiological framework.[14]

Among the established risk factors for CIN, diabetes mellitus markedly increases the likelihood of CIN development in patients with pre-existing chronic kidney disease. This is mainly attributed to the increased susceptibility of the diabetic kidney to oxidative stress and hypoxia.[15,16] However, in this study, diabetes was not identified as an independent risk factor for CIN. This may suggest that the risk associated with diabetes is overshadowed by other comorbidities such as advanced age, heart failure, and impaired renal function.

Another important finding relates to hyperuricemia, which has been shown in meta-analyses to increase the risk of CIN by approximately twofold and serve as an independent predictor.[17] Elevated uric acid has been linked to endothelial dysfunction, inflammation, and enhanced oxidative stress.[18] It is frequently seen in individuals with renal impairment due to the kidney's key role in uric acid excretion.[19] Consistent with these findings, this study also identified hyperuricemia as an important risk factor for the development of CIN.

Interestingly, despite previous findings showing a negative correlation between hyperuricemia and antioxidant capacity, such as in studies using the oxidative balance score (OBS), the results suggest a different relationship.[20] In contrast, this study demonstrated a positive correlation between hyperuricemia and total antioxidant status (TAS), which appears to contradict the former findings. However, in a study conducted among patients with early-onset hyperuricemia, uric acid was shown to be associated with oxidative stress, inflammation, and the inflammatory response, supporting the potential antioxidant role of uric acid observed in this cohort.[21] Uric acid has been identified as one of the most important natural antioxidants, acting as a free radical scavenger.[22] However, the authors found no significant association between uric acid and other oxidative stress markers, such as TOS, OSI, or 8-OHdG levels.

Reactive oxygen species (ROS) play a critical role in the pathogenesis of CIN. In a study by Börekçi et al[23], the relationship between TAS, TOS, OSI, and oxidative stress was investigated in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous intervention who subsequently developed CIN. In the CIN group, TAS was significantly lower, whereas TOS and OSI levels were significantly higher. Logistic regression analysis further identified OSI as an independent predictor of CIN. In contrast to previous studies reporting decreased TAS and increased TOS and OSI levels in patients developing CIN, the findings demonstrated a different pattern. In this study, TAS levels measured after CAG were higher in the CIN group, whereas no significant differences were observed in TOS and OSI levels between the groups. In addition, post-procedural 8-OHdG levels did not significantly differ between patients with and without CIN. Therefore, the observed increase in TAS should be interpreted with caution and should not be considered definitive evidence of reduced oxidative injury or effective antioxidant protection. Rather, it may reflect a possible adaptive or compensatory antioxidant response to contrast-related renal stress. Given the dynamic and multifactorial nature of oxidative stress responses, this interpretation requires confirmation in larger studies with serial biomarker measurements.

In this study, a positive correlation was observed between uric acid levels and TAS, suggesting that both parameters may increase in parallel as part of the antioxidant response. However, this association does not imply a causal relationship and should be interpreted with caution.

Another important consideration is the timing of biomarker measurements. In the present study, oxidative stress markers and 8-OHdG levels were measured at baseline and 72 hours after contrast exposure. The 72-hour time point was selected because it falls within the conventional 48–72-hour diagnostic window commonly used in CIN studies and provides clinically relevant information regarding sustained biomarker changes associated with renal injury. In addition, a considerable proportion of patients underwent coronary angiography as outpatients or were discharged early after the procedure, which limited the feasibility of obtaining additional blood samples at 24 or 48 hours. Nevertheless, because oxidative stress responses may be dynamic after contrast administration, future studies including serial biomarker measurements at earlier time points may provide a more detailed characterization of the temporal oxidative stress response after contrast exposure.

Furthermore, the absence of significant differences in TOS and OSI levels may indicate a preserved redox balance, in which increased antioxidant capacity offsets potential oxidative damage.

In addition, the heterogeneity of prophylactic strategies may have influenced oxidative stress responses and should be considered when interpreting the present findings. Preventive measures, including intravenous hydration with isotonic saline or sodium bicarbonate-based solutions, N-acetylcysteine, statin therapy, or combinations of these approaches, were not administered according to a predefined, standardized study protocol. Instead, they were organized by the cardiology team in accordance with institutional practice and individualized patient risk assessment. More intensive or combination-based prophylactic approaches were more likely to be used in patients with higher clinical risk, particularly those with impaired renal function, diabetes mellitus, advanced age, or heart failure. Therefore, the effects of preventive interventions cannot be clearly separated from the underlying risk profile of the patients, and this heterogeneity may represent a potential confounding factor for both CIN development and oxidative stress parameters.

In addition to systemic oxidative stress markers, the authors also evaluated 8-hydroxy-2'-deoxyguanosine (8-OHdG), a well-established marker of DNA damage due to oxidative stress. In a study evaluating the association between CKD and oxidative stress markers, 8-OHdG was found to be inversely correlated with creatinine clearance.[24] Similarly, another study comparing CKD patients on hemodialysis (HD), CKD patients not receiving HD, and the healthy individuals demonstrated that the highest levels of 8-OHdG were observed in HD-treated CKD patients.[25] Evidence regarding the association of acute kidney injury with 8-OHdG is limited; however, a study reported increased 8-OHdG levels in cases of acute renal failure following snake envenomation.[26] Oxidative stress has been suggested in the literature as a major determinant of CIN development. In this study, a significant reduction in 8-OHdG levels was observed in the control group, whereas no statistically significant increase in DNA damage was detected in patients who developed CIN. To the best of the knowledge, this is one of the few studies evaluating DNA damage in relation to CIN using 8-OHdG levels. The absence of a significant increase in 8-OHdG levels in the CIN group may be explained by several factors. First, biomarker measurements were obtained at baseline and 72 hours after contrast exposure, which may not have captured early and transient changes in oxidative DNA damage. Second, the use of low-osmolar, non-ionic contrast agents in this cohort may have attenuated oxidative injury, thereby limiting detectable DNA damage.

Finally, studies assessing the relationship between percutaneous coronary intervention and oxidative stress parameters have generally reported increases in TOS and OSI and decrease in TAS after the procedure.[27] Interestingly, this study did not confirm these findings, as no significant differences in oxidative stress parameters were observed between patients who underwent intervention and those who did not. This discrepancy may suggest that revascularization itself could reduce oxidative burden, thereby exerting a protective effect.

Study Limitations

This study has several limitations. First, prophylactic strategies for CIN prevention were not standardized. Although periprocedural preventive measures were applied according to institutional practice and individualized clinical assessment, the type, timing, and combination of prophylactic interventions varied among patients. Intravenous hydration, sodium bicarbonate-based hydration, oral N-acetylcysteine, statin therapy, or their combinations may have influenced both the development of CIN and the measured oxidative stress parameters. Therefore, this heterogeneity should be considered a potential confounding factor.

Second, biomarker measurements were performed at baseline and 72 hours after contrast exposure. Although the 72-hour assessment is compatible with the conventional 48–72-hour diagnostic window used in CIN studies, earlier measurements at 24 or 48 hours could not be routinely obtained because many patients were managed as outpatients or discharged early after coronary angiography. Therefore, the temporal pattern of early oxidative stress responses and oxidative DNA damage could not be fully evaluated.

Finally, the study was designed to compare patients with and without CIN rather than to estimate the incidence of CIN in the overall coronary angiography population. Therefore, the proportion of CIN cases in the study sample reflects the predefined sampling strategy and should not be interpreted as the incidence of CIN among all patients undergoing coronary angiography.

CONCLUSION

This study is one of the few to evaluate oxidative stress and DNA damage, as assessed by 8-OHdG levels, in patients who developed contrast-induced nephropathy (CIN). Advanced age and heart failure were identified as the strongest predictors of CIN, while other variables such as uric acid, hypertension, CKD, and anemia were also significantly associated. The positive association between serum uric acid levels and TAS may reflect a parallel change in antioxidant capacity; however, this observational finding does not establish a causal relationship. Although previous studies have demonstrated an important role of oxidative stress in the pathogenesis of CIN, the authors did not observe a strong association between oxidative stress parameters and CIN in this cohort. The post-CAG increase in TAS levels and reduction in TOS levels may indicate a compensatory antioxidant response to contrast exposure. No significant increase in 8-OHdG was observed in the CIN group, which may be attributed either to the use of modern contrast agents with lower doses and reduced toxicity or to limitations in detecting DNA damage in the early period. In this context, further studies with larger sample sizes and longer follow-up are warranted to better clarify the relationship between oxidative stress, DNA damage, and CIN development.

Ethics Committee Approval: This study was approved by the Ethics Committee of Eskişehir Osmangazi University (Approval No: 41, Date: February 4, 2021).

Artificial Intelligence Usage Statement: During the preparation of this manuscript, an artificial intelligence–based tool (ChatGPT, OpenAI) was used in a limited manner only for language editing, grammar checking, and improving textual clarity. Artificial intelligence was not used for generating scientific content, data analysis, interpretation of results, or any methodological components of the study. All scientific interpretations, analyses, and conclusions were independently developed and verified by the author(s).

Informed Consent: Written informed consent was obtained from all patients who agreed to participate in the study.

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