Exploring the Impact of Contrast-Induced Nephropathy on NRF2 Expression in Renal Tissues of Wistar Rats: A Pathway to Oxidative Stress Modulation

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KEYWORDS

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ABSTRACT:

Introduction: Contrast-Induced Nephropathy (CIN) is a form of acute kidney injury that arises following the administration of intravascular contrast agents. The increasing use of contrast agents in medical practice raises the incidence of CIN, which is associated with complications, prolonged hospitalization, and increased mortality. Nuclear Factor Erythroid Related Factor-2 (NRF2) plays a critical role in antioxidant and anti-inflammatory responses, making it a potential therapeutic target to mitigate CIN.

Objectives: This study aimed to evaluate the temporal changes in NRF2 expression in renal tissues following contrast media administration in a rat model.

Methods: Twenty-four male Wistar rats (Rattus norvegicus), aged 2-3 months, were divided into four groups: one control group and three intervention groups, which received Iopromide (370 mg iodine/mL) at a dose of 1600 mg iodine/kg body weight. NRF2 expression was assessed by immunohistochemistry using H-Score analysis, which quantifies the intensity and percentage of positive cells in glomeruli, tubules, and intrarenal vasculature, at 24, 48, and 72 hours post-injection. Statistical analysis was performed using SPSS, including homogeneity and normality tests, followed by one-way ANOVA and LSD post hoc tests.

Results: NRF2 expression showed no significant change in the glomerulus and intrarenal vasculature ($p = 0.660$ and $p = 0.075$, respectively). NRF2 expression in the renal tubules exhibited significant differences ($p < 0.001$) at 24 and 48 hours, but returned to baseline at 72 hours ($p = 0.902$).

Conclusions: NRF2 expression remained stable in the glomerulus and intrarenal vasculature, while renal tubule NRF2 expression increased significantly at 24 and 48 hours, suggesting a potential early protective response. These findings highlight the temporal dynamics of NRF2 activation and its potential therapeutic implications in preventing CIN.

INTRODUCTION:

Contrast-Induced Nephropathy (CIN) is a significant form of acute kidney injury (AKI) that occurs following the administration of intravascular contrast agents during medical imaging or interventional procedures. CIN presents a major clinical challenge, as it can lead to severe patient outcomes, including prolonged hospital stays, increased healthcare costs, and higher mortality rates (Sůva et al., 2022; Wang et al., 2017). The expanding use of contrast media in diagnostic and therapeutic procedures has made it essential to better understand the incidence of CIN and to develop effective preventive strategies. Despite advances in care, current therapies for CIN, primarily focused on non-dialytic approaches, remain limited, highlighting the urgent need for more effective prevention and treatment options (Marenzi et al., 2011).

The rising reliance on contrast agents in modern medical practice underscores the importance of managing their associated risks. Over the past two decades, there has been an 800% increase in the use of computed tomography (CT) scans and a 390% rise in cardiac catheterization procedures (Hiremath & Modi, 2017; Wang et al., 2017). While these advancements have significantly improved diagnostic and therapeutic outcomes, they have also contributed to a marked increase in CIN cases, particularly among high-risk groups such as those with preexisting renal conditions, diabetes, hypertension, or chronic kidney disease (CKD) (Rubio-Navarro & Riera, 2019). Estimates suggest that CIN affects 2% to 30% of patients, with the incidence being especially high in these vulnerable populations. Although many cases resolve within weeks, CIN remains a major concern due to its potential to cause irreversible renal damage and long-term health complications (Rubio-Navarro & Riera, 2019; Sůva et al., 2022).

Emerging evidence has highlighted Nuclear Factor Erythroid Related Factor 2 (NRF2) as a promising biomarker for CIN. NRF2 plays a crucial role in cellular defense mechanisms, particularly in protecting against oxidative stress and inflammation—two key contributors to renal injury in CIN (Reddy & Huang, 2015). NRF2 is involved in regulating various cellular processes, including the modulation of immune responses, antioxidant activities, and the inflammatory response in a variety of pathological conditions (Huang, 2014). Specifically, NRF2 activation has been shown to enhance the expression of genes involved in protecting against oxidative stress, which plays a central role in the pathogenesis of CIN. These findings suggest that NRF2 may serve as a therapeutic target for protecting kidney function and mitigating damage caused by oxidative stress and inflammation in CIN and other related disorders (Khor, 2008; Kobayashi, 2013).

Given the increasing use of contrast agents and their well-documented adverse effects on kidney health, understanding the underlying molecular and cellular mechanisms of CIN is of paramount importance (Reddy & Huang, 2015; Rubio-Navarro & Riera, 2019). CIN results from a combination of direct renal tubular toxicity, endothelial dysfunction, and renal ischemia, often exacerbated by oxidative stress induced by contrast agents. Investigating strategies such as preconditioning or targeted therapies aimed at enhancing NRF2 expression may offer novel avenues for safeguarding renal function in CIN patients (Huang, 2014). The aim of this study is to

explore the protective role of NRF2 in a rat model of CIN induced by the contrast agent loperamide. This research could potentially lead to novel therapeutic approaches for preventing or mitigating CIN, ultimately improving patient outcomes.

METHODOLOGY:

Study Design

This study employed a true experimental research methodology using a post-test-only control group design. The primary aim was to evaluate the impact of loperamide contrast agent administration on NRF2 expression in renal tissues in a rat model. A sample of 24 male Wistar rats (Rattus norvegicus) were used, with rats evenly distributed across four groups (six rats per group). The experimental groups (K1, K2, K3) received the contrast agent Iopromide, while the control group (K0) received no treatment.

The time points for NRF2 expression evaluation were 24 hours (K1), 48 hours (K2), and 72 hours (K3) post-injection. Immunohistochemical assessment was employed to measure NRF2 expression across three renal tissue structures: the glomerulus, renal tubules, and intrarenal vasculature. The expression levels were quantified using H-scores derived from immunohistochemical staining. Ethical approval for animal experimentation was obtained under ethical number 97/EC/KEPK/FKUA/2024.

Samples Collection

Male Wistar rats aged 2-3 months and weighing between 100-200 grams were selected for this experiment. These criteria were chosen to ensure a homogenous population with minimal variability in developmental stage and size. All rats were obtained from previous studies conducted at the Department of Pathological Anatomy, which adhered to strict ethical guidelines.

The contrast agent administered was **Iopromide** (370 mg iodine/mL), a commonly used contrast media. The injection dose was determined based on iodine equivalent doses, specifically 1600 mg iodine per kg of body weight. The rats were euthanized at the designated time points: 24, 48, and 72 hours post-injection to examine the temporal effects on NRF2 expression.

At each time point, the kidneys were harvested, and the tissue samples were embedded in paraffin blocks for subsequent histological analysis. Thin sections of kidney tissue (5 µm in thickness) were cut from the paraffin blocks, deparaffinized, and rehydrated. Immunohistochemical staining was performed to detect and quantify NRF2-positive cells within the glomeruli, tubules, and intrarenal vasculature. The percentage of NRF2-positive cells was determined by analyzing the immunohistochemical labelling under a light microscope.

Statistical Analysis

Data analysis was conducted using SPSS software (version X), and results were expressed as mean ± standard deviation (SD). Normality of the data was assessed using the Shapiro-Wilk or

Kolmogorov-Smirnov tests. To assess homogeneity of variance across groups, Levene's test was used.

For datasets exhibiting normal distribution and homogenous variances, one-way ANOVA was employed to compare means between groups. In the case of significant differences indicated by ANOVA ($p < 0.05$), Tukey's post-hoc test was performed to identify which groups differed from each other.

For non-normally distributed data, the Kruskal-Wallis test was utilized as a non-parametric alternative to ANOVA for comparing group medians. The significance level for all statistical tests was set at $p < 0.05$, ensuring a robust and rigorous analysis.

RESULTS:

This study investigated the expression of NRF2 in the kidneys of male Wistar rats (Rattus norvegicus), aged 2 to 3 months and weighing between 100 and 200 grams. The rats were divided into four experimental groups: one control group (K0) and three intervention groups (K1, K2, and K3). Each group consisted of six rats, providing a balanced and structured approach to address the research objectives. Immunohistochemical analysis using the Histochemical Scoring Assessment (H-Score) method was performed, focusing on three specific kidney regions: the glomerulus, intrarenal vasculature, and tubules (Figures 1-3).

Before conducting statistical tests, homogeneity and normality checks confirmed that the data from all groups were similarly distributed and normally spread. This validated the use of one-way ANOVA as the appropriate statistical method for comparison.

Glomerulus

In the analysis of NRF2 expression within the glomerulus, there were no significant differences between the four groups ($p = 0.660$), as shown in **Table 1** and **Figure 1** and **Figure 2**. The data suggest that NRF2 expression remained relatively stable across both the control and intervention groups. These results indicate that the experimental interventions did not substantially alter NRF2 expression in the glomerular region.

Intrarenal Vasculature

In the intrarenal vasculature, NRF2 expression showed some variation across the groups, but statistical analysis revealed no significant differences ($p = 0.075$) (**Table 2, Figure 4**). **Figure 3** illustrates varying intensities of NRF2 expression across the experimental groups, with some groups showing stronger staining compared to others. However, the lack of statistically significant differences suggests that the interventions did not affect NRF2 expression in the vascular area.

Renal Tubules

A significant difference in NRF2 expression was observed in the renal tubules ($p < 0.001$) (**Table 3**). Post hoc LSD testing provided further insight into the specific intergroup differences. The control group (K0) had significantly lower levels of NRF2 expression compared to intervention groups K1 ($p = 0.0003$) and K3 ($p = 0.9993$), as shown in **Table 4** and **Figure 5**. This

indicates that the interventions applied to groups K1 and K3 significantly affected NRF2 expression in the renal tubules.

Notably, comparisons between the intervention groups also revealed the following: K1 versus K2 showed a marginally significant difference ($p = 0.0550$); K1 versus K3 showed a highly significant difference ($p < 0.0002$); and K2 versus K3 showed a significant difference ($p = 0.0902$). The comparison of the control group (K0) and intervention group K3 showed no significant difference ($p = 0.9993$), suggesting that the intervention applied to group K3 may have effectively normalized NRF2 expression levels, rendering them comparable to the baseline control group (**Tables 3 and 4**, **Figure 6 and 7**).

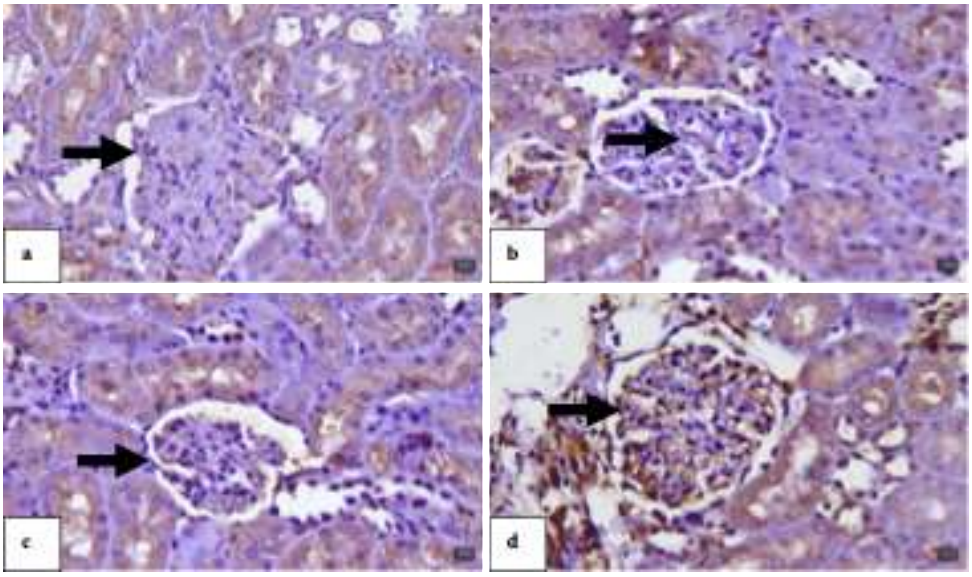

Figure 1. Overview of NRF2 expression in the glomerulus: a. Negative intensity, b. Weak intensity, c. Moderate intensity, d. Strong intensity. Arrows indicate NRF2 expression.

Table 1. NRF2 Expression in the Glomerulus (Source: Authors)

Group	Mean ± SD	Normality	p value
K0	90,00 ± 33,46	0,245	
K1	140,00 ± 31,62	0,762	0,660
K2	101,67 ± 67,35	0,690	
K3	75,00 ± 48,47	0,884	

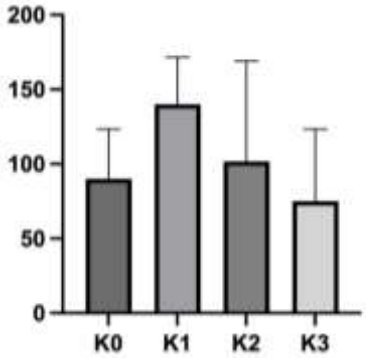

Figure 2. NRF2 Expression in the Glomerulus Across K0, K1, K2, and K3 Groups

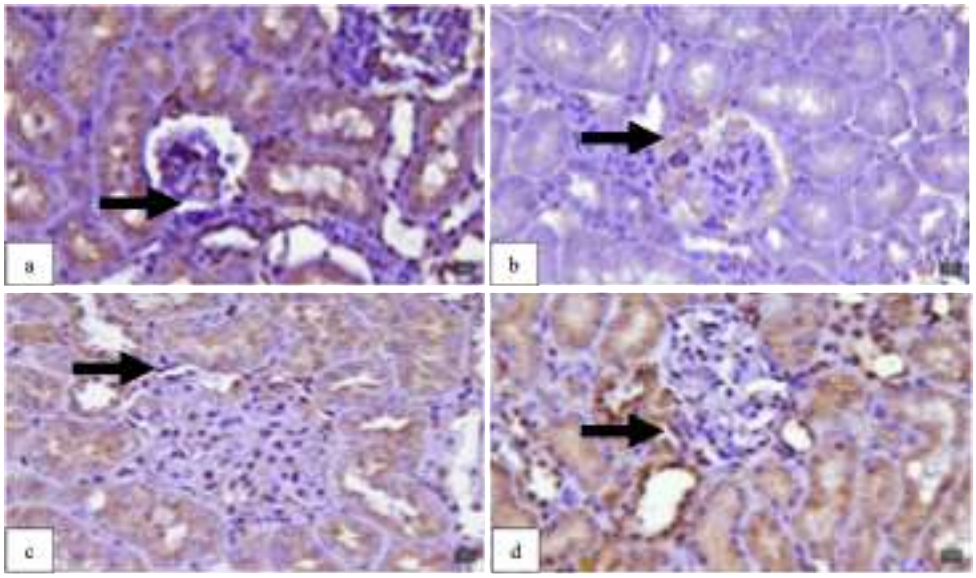

Figure 3. Overview of NRF2 expression in the intrarenal vasculature: a. Negative intensity, b. Weak intensity, c. Moderate intensity, d. Strong intensity. Arrows indicate NRF2 expression.

Table 2. NRF2 Expression in the Intrarenal Vasculature (Source: Authors)

Group	Mean ± SD	Normality	p value
K0	106,67 ± 33,26	0,946	0,075
K1	171,67 ± 66,76	0,645	
K2	138,33 ± 53,82	0,707	
K3	68,87 ± 31,25	0,939	

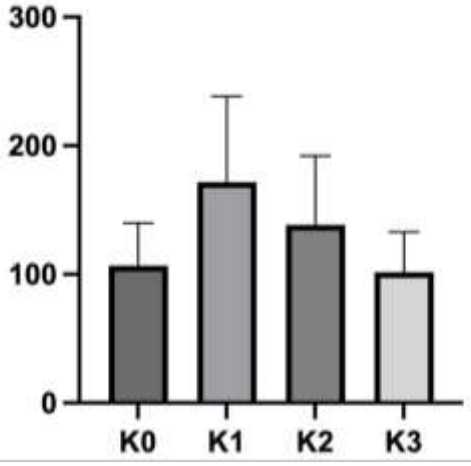

Figure 4. NRF2 Expression in the Intrarenal Vasculature Across K0, K1, K2, and K3 Groups

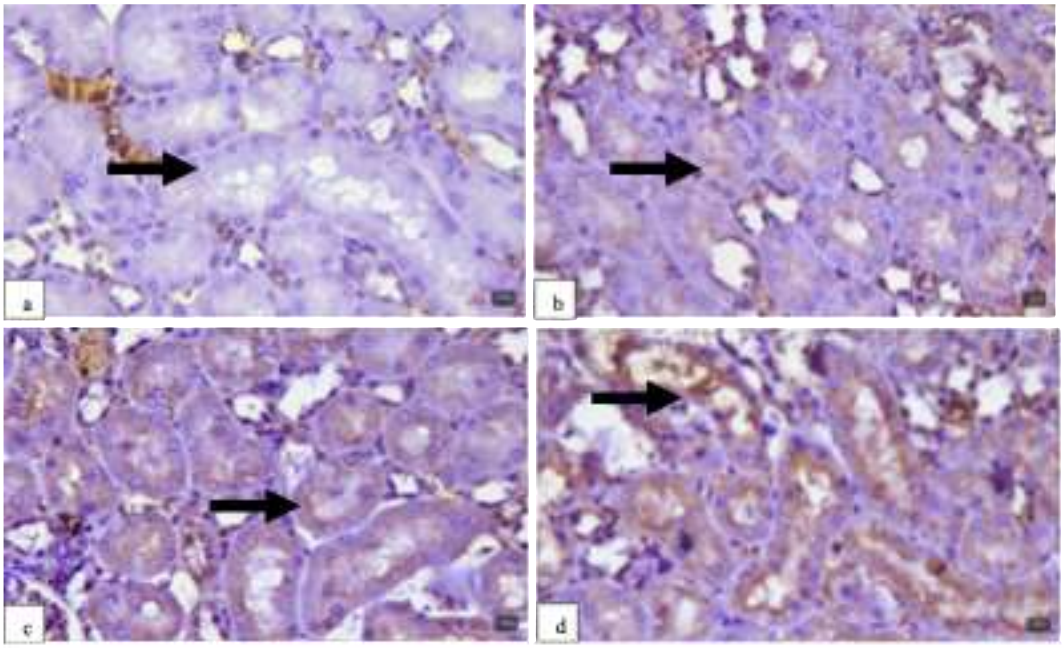

Figure 5. Overview of NRF2 expression in the renal tubule: a. Negative intensity, b. Weak intensity, c. Moderate intensity, d. Strong intensity. Arrows indicate NRF2 expression.

Table 3. NRF2 Expression in the Renal Tubule (Source: Authors)

Group	Mean ± SD	Normality	p value
K0	113,33 ± 17,51	0,918	< 0,001
K1	181,67 ± 24,01	0,158	
K2	145,00 ± 28,80	0,913	
K3	111,67 ± 20,41	0,081	

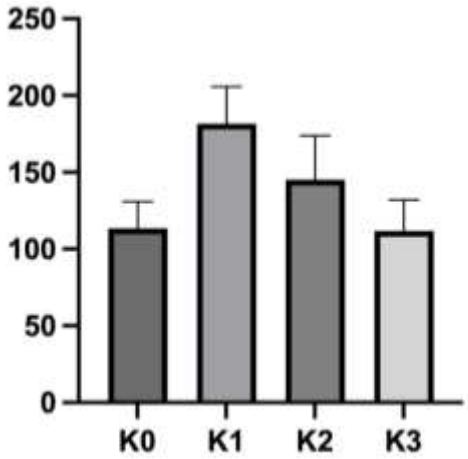

Figure 6. NRF2 Expression in the Renal Tubule Across K0, K1, K2, and K3 Groups

Table 4. Post Hoc LSD Test Analysis between groups for NRF2 Expression in the Renal Tubule (Source: Authors)

	K0	K1	K2	K3
K0		0,0003	0,1142	0,9993
K1	0,0003		0,0550	0,0002
K2	0,1142	0,0550		0,0902
K3	0,9993	0,0002	0,0902	

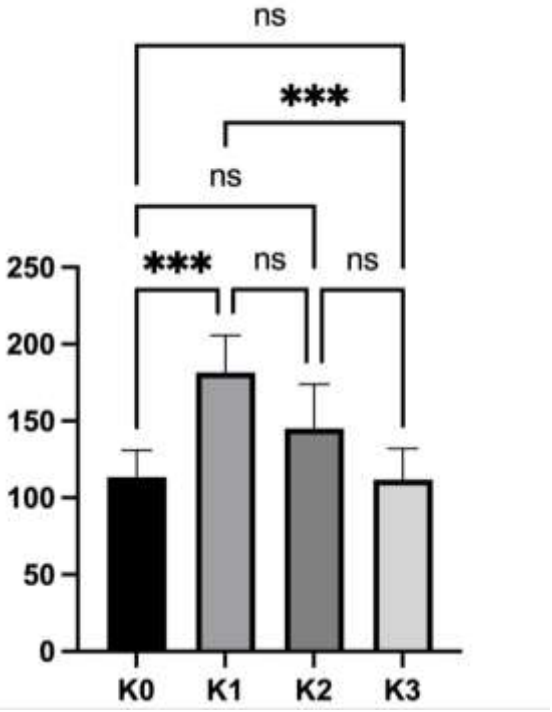

Figure 7. Post hoc LSD test analysis between groups for NRF2 expression in the renal tubule (***: p<0,05)

DISCUSSION:

The kidneys are crucial in maintaining homeostasis, and their dysfunction during CIN can lead to significant renal impairment. These functions rely on the integrity of renal structures, particularly the glomerulus, tubules, and vasculature. ICM exposure is a well-known risk factor for Contrast-Induced Nephropathy (CIN), a major cause of acute kidney injury (Brooks & Hoorn, 2024). CIN, typically identified by an increase in serum creatinine levels 48–72 hours post-contrast administration, remains a major clinical concern due to its potential to lead to severe renal dysfunction and increased mortality risk (Zhang et al., 2024).

The pathogenesis of CIN is fundamentally linked to oxidative stress, which results from the generation of reactive oxygen species (ROS) following ICM administration. ROS production disrupts cellular homeostasis, causing inflammation and damage to renal tubular cells, ultimately leading to apoptosis, necrosis, and ferroptosis (Tochaikul et al., 2024). In this context, the Keap1-NRF2-ARE pathway is critical in defending against oxidative damage. NRF2, a key transcription factor, regulates antioxidant genes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and NAD(P)H quinone dehydrogenase 1 (NQO1) (Ran et al., 2024; Sendeski et al., 2012). Under oxidative stress, NRF2 is activated through the disruption of its interaction with Keap1, allowing its translocation to the nucleus where it activates the expression of protective genes (Ran et al., 2024; Sendeski et al., 2012). Recent studies employing rat models have shown the dynamic temporal expression of NRF2 in response to CIN, underlining its essential role in mitigating renal injury (Zhou et al., 2019).

In this study, we investigated NRF2 expression in Wistar rats exposed to ICM-induced stress, particularly focusing on the temporal dynamics of NRF2 expression in different kidney regions. Our results showed that NRF2 expression in renal tubules peaked at 24 hours post-

exposure, indicating a rapid protective response to oxidative stress. This aligns with previous studies showing that early NRF2 activation is critical for defending against ICM-induced renal damage (Zhou et al., 2019), (Du et al., 2024). However, we also observed a decline in NRF2 expression after 48 hours, reaching its lowest levels at 72 hours. This temporal reduction may reflect cellular adaptation or depletion of antioxidant resources, suggesting that prolonged oxidative stress may overwhelm the NRF2-mediated defense mechanism (Liu & Daneshgari, 2006).

NRF2 expression in the glomerulus remained stable with no significant differences between the groups, possibly indicating stronger adaptive mechanisms in this region (Du et al., 2024). This suggests the glomerulus may have stronger adaptive mechanisms or a higher threshold for oxidative damage than the renal tubules (Du et al., 2024). Previous studies have indicated that the glomerulus may have a higher threshold for oxidative stress, meaning that it requires more substantial injury to induce a significant NRF2 response (Du et al., 2024), (Gao et al., 2022). This could explain the observed minimal change in NRF2 expression in this region, even after exposure to ICM.

Similar to the renal tubules, NRF2 expression in the intrarenal vasculature increased initially and then normalized. This suggests that the intrarenal vasculature is also responsive to oxidative stress, but its recovery may occur more slowly compared to the tubules. Previous studies have shown that the vasculature, particularly the endothelial cells, is affected by ICM-induced oxidative stress, which impacts vascular tone and integrity (Gao et al., 2022). These results indicate that the intrarenal vasculature is susceptible to ICM-induced damage, but recovery may occur more slowly than in the renal tubules.

NRF2 also protects against ferroptosis, a form of cell death triggered by lipid peroxidation, which is crucial in CIN (Trotta et al., 2024). Ferroptosis is a key pathway in CIN, and NRF2 activation has been shown to suppress this form of cell death, thereby protecting renal cells from damage. The Sirt6/NRF2/GPX4 pathway has been identified as a critical mechanism in alleviating ferroptosis in kidney cells, further highlighting the importance of NRF2 in protecting against CIN-induced injury (Trotta et al., 2024), (Zhao et al., 2016). However, NRF2 activation may not be uniformly effective across all individuals. Conditions such as diabetes and hypertension can impair NRF2's ability to respond to oxidative stress, thereby increasing the susceptibility of these individuals to CIN (Wilmes et al., 2011). This emphasizes the need to optimize NRF2 activation for maximal therapeutic benefit, as excessive or insufficient NRF2 activity may have detrimental effects (Khaleel et al., 2023).

Our findings are consistent with the work of Zhou et al. (2019), who demonstrated that tert-butylhydroquinone (t-BHQ) activated NRF2 and reduced ROS levels within 24 hours of CIN induction, similarly to the rapid NRF2 activation observed in our study (Zhou et al., 2019). Khaleel et al. (2023) also reported swift NRF2 activation following lansoprazole administration, which alleviated oxidative stress within 3 hours of ICM exposure (Jiang et al., 2020). Furthermore, studies by Ma et al. (2023) emphasized the protective role of NRF2, as NRF2 knockdown in animal models resulted in intensified renal injury, underlining the critical function of NRF2 in safeguarding against ROS-induced damage (Li et al., 2023). However, Zhao et al. (2016) pointed out that while NRF2 activation mitigated oxidative damage, additional protective pathways were necessary for complete renal protection, suggesting that NRF2 activation alone may not be sufficient for full protection (Kim et al., 2022).

The clinical implications of these findings are profound. Pharmacological interventions that activate NRF2 or inhibit Keap1 may improve kidney antioxidant defenses, mitigating ROS-induced damage and preventing ferroptosis in CIN. Our results indicate that early intervention is crucial to optimize NRF2's protective effects, which is consistent with previous studies suggesting that NRF2 activation is most beneficial when initiated early in the course of CIN. Future research should focus on refining NRF2-targeted therapies, considering individual risk factors such as comorbidities (e.g., diabetes, hypertension) that can impair NRF2 activation. Additionally, investigations into the duration of oxidative stress and the optimal timing for NRF2 intervention are essential to further enhance therapeutic outcomes and reduce kidney damage in at-risk populations.

CONCLUSION:

This study highlights the essential role of NRF2 in protecting renal tissues from oxidative stress during CIN administration. NRF2 expression showed significant changes in the renal tubules, indicating an acute protective response followed by adaptation or normalization, while expression in the glomerulus and intrarenal vasculature remained stable. These findings suggest that targeting the Keap1-NRF2-ARE pathway could enhance antioxidant defenses, mitigate oxidative damage, and provide a therapeutic approach to protecting kidney function in CIN. Early intervention may be key to maximizing NRF2's protective effects

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