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Correlation Between Nitrogenous Waste Products and Prooxidant-Antioxidant System Parameters in Patients with Glomerulonephritis

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Abstract. *Chronic kidney diseases, particularly glomerulonephritis (GN), continue to represent a major global public health challenge. The progression of GN is heavily driven by escalating uremic intoxication, which exacerbates oxidative stress and provokes profound cellular pathogenic damage. Consequently, the primary objective of this study was to explore the pathogenetic interactions between end-products of nitrogen metabolism and the prooxidant-antioxidant network across various stages of chronic renal failure in GN patients. To achieve this, a cohort comprising 50 individuals diagnosed with GN (aged 30–80 years), divided into a conservative non-dialysis group (n = 21) and a terminal hemodialysis group (n = 29), along with 10 healthy controls, was recruited. Serum samples from all participants were analyzed using biochemical and spectrophotometric assays to quantify urea and uric acid concentrations, alongside lipid peroxidation (MDA) and antioxidant defense biomarkers (GSH and CAT). Our findings reveal that the advancement of the disease and the deepening of uremic toxicity significantly accelerate oxidative stress, culminating in a severe depletion of antioxidant defense mechanisms during the terminal stage. Therefore, the concurrent monitoring of these biochemical indices holds substantial prognostic value in clinical settings.*

Keywords: *glomerulonephritis, uremic intoxication, urea, oxidative stress, malondialdehyde, catalase, reduced glutathione*

Introduction

Currently, glomerulonephritis (GN) represents a profound global health challenge, serving as a primary driver for the development of chronic kidney disease (CKD) and its end-stage counterpart. Affecting millions worldwide, this pathology consistently ranks among the leading factors contributing to end-stage renal disease (GBD Chronic Kidney Disease Collaboration, 2020; Kramer et al., 2021). As the disease progresses, the deterioration of renal filtration capacity precipitates a pathological accumulation of nitrogenous metabolic end-products in the bloodstream, culminating in severe uremic intoxication (Dounousi et al., 2006).

Fundamental research indicates that the uremic milieu goes beyond the mere mechanical retention of metabolites; it acts as an aggressive pathogenetic trigger for the massive release of free radicals within the body (Himmelfarb et al., 2002; Liakopoulos et al., 2017).

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The chronic inflammatory state and mitochondrial dysfunction inherent to GN lead to the unchecked generation of reactive oxygen species (ROS) and the establishment of severe oxidative stress (Bhatia et al., 2020). Because these radicals primarily target the phospholipid bilayers of cellular membranes, the process of lipid peroxidation (LPO) is acutely accelerated (Manful et al., 2025).

Malondialdehyde (MDA), one of the most toxic terminal products of LPO, is highly reactive and capable of denaturing renal architectures while inducing cellular death (Ayala et al., 2014; Niedernhofer et al., 2003). Concurrently, the pathogenetic involvement of uric acid—a residual product of purine metabolism—warrants particular scientific attention. Although it exhibits antioxidant properties under physiological conditions, the backdrop of uremic hyperuricemia forces uric acid to alter its nature, functioning instead as a potent prooxidant that further exacerbates oxidative injuries (Sautin & Johnson, 2008).

To counteract oxidative damage, the human body mobilizes a sophisticated antioxidant defense network. Reduced glutathione (GSH), the most crucial non-enzymatic component of this system, directly scavenges and neutralizes free radicals; however, its reserves are rapidly exhausted under conditions of chronic stress and inflammation (He & Shi, 2023; Rai et al., 2021). On the other hand, catalase, a fundamental element of the enzymatic defense, shields cells by detoxifying harmful hydrogen peroxide (Aladyeva & Zimatkin, 2022; Hong & Park, 2021).

In light of these dynamics, a comprehensive evaluation of how uremic intoxication impacts oxidative damage and the eventual exhaustion of compensatory mechanisms holds substantial clinical relevance. Such insights are essential not only for unraveling the developmental mechanisms of renal pathologies but also for conceptualizing and designing novel, targeted antioxidant therapeutic strategies.

Materials and Methods

This research enrolled a cohort of 50 patients diagnosed with glomerulonephritis, aged between 30 and 80 years, comprising 27 females (54%) and 23 males (46%). A control group consisting of 10 apparently healthy individuals within a matched age bracket was also included. Based on their clinical status, the patients were stratified into two primary cohorts: the first group consisted of 21 patients in the conservative, non-dialysis stage of the disease, while the second group comprised 29 terminal-stage patients undergoing regular hemodialysis. Blood samples obtained from all participants were utilized to evaluate uremic intoxication markers—serving as indicators of renal functional capacity—alongside parameters of lipid peroxidation (LPO) and the antioxidant defense system (AOS). Serum urea levels were quantified utilizing the classical colorimetric Fearon assay, which relies on a direct chemical interaction with diacetyl monoxime. Conversely, uric acid concentrations were determined via a specific enzymatic uricase-peroxidase (Trinder reaction) colorimetric method.

To ascertain the extent of cellular injury and oxidative stress, LPO and AOS indicators were evaluated using spectrophotometric techniques. The serum concentration of malondialdehyde (MDA), the principal end-product of lipid peroxidation, was measured using the conventional method based on its reaction with thiobarbituric acid (TBA) under elevated temperatures and acidic conditions. For the analysis of antioxidant system elements, the level of reduced glutathione (GSH) was determined colorimetrically through the specific reaction of free sulfhydryl groups with Ellman's reagent (DTNB). Concurrently, catalase enzyme activity was assessed in erythrocyte hemolysates based on the principle of measuring the hydrogen peroxide decomposition rate.

All numerical data acquired during the study were processed using Microsoft Excel software, in accordance with modern biomedical statistical guidelines. For each analyzed biochemical parameter,

the arithmetic mean and its standard error (M ± m) were calculated. The statistical significance of intergroup variances (among the control, conservative, and terminal groups) was evaluated using the parametric Student's t-test, with findings deemed statistically reliable at probability thresholds of $p < 0.05$, $p < 0.01$, and $p < 0.001$. Furthermore, Pearson's correlation analysis (r) was applied to determine the direction and magnitude of the reciprocal associations between uremic intoxication markers, cellular damage indices, and antioxidant defense components.

Results

To evaluate the excretory capacity of the kidneys, the serum concentrations of urea and uric acid were measured in the enrolled glomerulonephritis patients across different stages of disease progression and subsequently compared with those of the healthy control cohort. The resulting quantitative data are summarized in Table 1.

Table 1
Comparative analysis of serum urea and uric acid levels between glomerulonephritis patients at various disease stages and the control group

Parameters	Control group	Conservative group (n = 21)	Terminal group (n = 29)	p-value
Uric acid mg/dL	3,9 ± 0,45	4,5 ± 0,58	7,34 ± 0,65	$p_1 > 0,05$ $p_2 < 0,001$ $p_3 < 0,001$
Urea mM/L	4,6 ± 0,7	15,4 ± 1,8	20,9 ± 2,3	$p_1 < 0,001$ $p_2 < 0,001$ $p_3 < 0,005$

Note. p_1 – significance of the difference between control and conservative groups; p_2 – between control and terminal groups; p_3 – between conservative and terminal groups.

As depicted in Table 1, the levels of nitrogenous metabolic end-products exhibited a significant elevation across both disease stages relative to the control group. Specifically, when compared to healthy subjects, urea concentrations surged by 3.3-fold ($p < 0.001$) in the conservative stage and approached an approximate 4.5-fold increase ($p < 0.001$) in the terminal hemodialysis group. Concurrently, uric acid levels demonstrated a sharp escalation, particularly during the terminal stage, exceeding control values by roughly 1.9-fold ($p < 0.001$).

To evaluate the cellular-level damage inflicted by this deepening uremic intoxication, parameters of lipid peroxidation (MDA) and the antioxidant defense system (GSH, CAT) were thoroughly investigated (Table 2).

Table 2
Intergroup comparative characteristics of LPO and AOS indicators in glomerulonephritis patients according to the disease stage

Parameters	Control group	Conservative group (n = 21)	Terminal group (n = 29)	p-value
MDA (nmol/mL)	2,85 ± 0,11	6,72 ± 0,13	7,91 ± 0,26	$p_1 < 0,001$ $p_2 < 0,001$ $p_3 < 0,001$
GSH (μmol/mL)	0,55 ± 0,026	0,39 ± 0,01	0,405 ± 0,021	$p_1 < 0,001$ $p_2 < 0,01$ $p_3 > 0,05$
CAT (U/mgHb)	18,5 ± 0,9	37,4 ± 2,4	10,7 ± 1,2	$p_1 < 0,001$ $p_2 < 0,001$ $p_3 < 0,001$

One of the most compelling findings of this study involves the dynamic trajectory of intracellular catalase activity. In the conservative stage, a 2.4-fold rise in MDA was accompanied by a compensatory twofold amplification in catalase activity (37.4 ± 2.4 U/mgHb; $p < 0.001$). However, as oxidative stress reached its peak during the terminal stage (MDA – 7.91 ± 0.26 nmol/mL), the antioxidant system underwent severe exhaustion. Consequently, catalase activity plummeted sharply, falling even below the baseline control levels (10.7 ± 1.2 U/mgHb).

To ascertain the direct impact of uremic toxins on the prooxidant-antioxidant balance, a Pearson correlation analysis was conducted among the investigated biochemical markers. The analysis revealed a moderate positive correlation between serum urea concentrations and MDA—the terminal product of lipid peroxidation—in both the non-dialysis conservative group ($r = +0.44$; $p < 0.05$) and the hemodialysis-dependent terminal group ($r = +0.49$; $p < 0.01$). Parallel to this, the elevation in urea was accompanied by a concurrent decline in GSH, the non-enzymatic component of the antioxidant system, across both cohorts ($r = -0.47$; $p < 0.05$ and $r = -0.41$; $p < 0.05$, respectively). Interestingly, the relationship between urea and the enzymatic antioxidant catalase shifted depending on the disease stage: a moderate positive correlation was recorded during the active compensatory phase of the conservative stage ($r = +0.44$; $p < 0.05$), whereas an inverse relationship emerged during the decompensated terminal stage ($r = -0.52$; $p < 0.01$).

Conversely, the associations between uric acid and oxidative stress indicators (MDA, GSH, and CAT) displayed a distinct dynamic. Although certain correlational trends were observed in both the conservative ($r = +0.36$, $r = -0.33$, $r = 0.32$) and terminal stages ($r = +0.31$, $r = -0.29$, $r = -0.33$), these numerical values failed to achieve statistical significance in either cohort ($p > 0.05$). This observation further corroborates that during glomerulonephritis, the primary burden of driving oxidative stress likely falls on other uremic toxins, such as urea, rather than uric acid.

Furthermore, the study evaluated the internal reciprocal dependencies among the elements of the prooxidant and antioxidant systems. The findings demonstrated that in the conservative non-dialysis group, the intensification of lipid peroxidation (MDA) led to a reduction in GSH ($r = -0.44$; $p < 0.05$) while simultaneously exhibiting a moderate positive correlation with CAT activity ($r = +0.46$; $p < 0.05$), indicating a protective cellular response. Nevertheless, this landscape altered drastically in the

terminal hemodialysis group; during this advanced stage, the surge in MDA displayed an inverse relationship with both GSH ($r = -0.52$; $p < 0.01$) and CAT ($r = -0.49$; $p < 0.01$), thereby confirming the complete collapse and exhaustion of the antioxidant defense network.

Discussion

The progression of glomerulonephritis is characterized by a continuous decline in the glomerular filtration rate and the consequent accumulation of nitrogenous metabolic end-products in the body. However, in clinical medicine, the uremic syndrome is recognized not merely as a mechanical retention of metabolites, but rather as a complex pathogenetic process that triggers severe metabolic dysfunctions at the cellular level, notably acute oxidative stress.

Our findings demonstrate that in both the conservative and terminal stages of the disease, the serum concentration of urea—a principal marker of nitrogen metabolism—rises sharply. Concurrently, uric acid levels exhibit an upward trend toward the upper limit in the terminal phase relative to the control group. This intensifying uremic environment induces an excessive generation of reactive oxygen species (ROS) within the organism. The assault of free radicals on the phospholipid bilayer of cell membranes accelerates the lipid peroxidation (LPO) process, a phenomenon corroborated in our study by the statistically significant elevation of MDA levels in both patient cohorts. The robust positive correlation observed between urea and MDA across both the conservative and terminal groups implies that the extent of oxidative damage is directly proportional not solely to urea, but to the overall magnitude of uremic intoxication.

To comprehend the pathogenetic mechanisms of oxidative stress, our most crucial discovery lies in the biphasic antioxidant response mounted by the body against prooxidant attacks. During the conservative stage of the disease, set against the backdrop of accelerated LPO, the nearly twofold amplification of intracellular catalase activity compared to the control group must be interpreted as a robust compensatory-adaptive mechanism. In other words, the cell maximally mobilizes its defensive front to neutralize the surging free radicals and hydrogen peroxide (H_2O_2) toxicity driven by the uremic milieu. This precisely explains the positive correlation registered between catalase, MDA, and urea during the conservative phase, indicating that the organism remains capable of combating oxidative stress. Nevertheless, the concurrent decline in the levels of GSH, a non-enzymatic antioxidant, signifies that these defensive reserves are already being partially depleted.

In the terminal stage, however, the chronicity of the process, the mounting uremic load, and the irreversible damage to renal tissue culminate in the complete collapse—or decompensation—of the antioxidant system. In this phase, alongside the further deepening of LPO, the persistently low levels of GSH coupled with the acute suppression of previously elevated catalase activity to levels below those of the controls, indicate that the system has reached a state of exhaustion. The inversion of the correlation between catalase, MDA, and urea into an inverse relationship within the terminal group serves as the mathematical and clinical proof of this profound antioxidant deficit.

Conclusion

The conducted research establishes that the impairment of renal function and the subsequent accumulation of nitrogenous waste products in patients with glomerulonephritis induce severe oxidative stress within the body. Throughout the developmental dynamics of the disease, the antioxidant defense system initially activates as a compensatory measure; however, it is entirely depleted by the profound impact of uremic intoxication in the terminal stage. The tight correlative links uncovered between the severity of renal failure, lipid peroxidation, and antioxidant indicators underscore that oxidative stress plays a pivotal role in the pathogenesis of chronic kidney diseases. Consequently, incorporating the assessment of the prooxidant-antioxidant status alongside traditional

uremic markers in the routine clinical management and monitoring of glomerulonephritis patients holds tremendous prognostic significance.

Declaration of Competing Interests

The authors declare that they have no competing interests.

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