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Renal Toxicity and Redox Imbalance: Novel Biomarkers Predicting Progression from Acute Kidney Injury to Chronic Kidney Disease

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ABSTRACT

Renal toxicity represents a major clinical and public health challenge, contributing substantially to the global burden of acute kidney injury and its frequent progression to chronic kidney disease. A growing body of research identifies oxidative stress and redox imbalance as central drivers of renal damage, modulating inflammation, tubular cell death, mitochondrial dysfunction, and maladaptive repair. During toxicant-induced kidney injury, excessive reactive oxygen species production overwhelms antioxidant systems, producing structural and functional alterations that often persist long after the initial insult. Recent technological advances in molecular profiling have revealed a new generation of biomarkers capable of detecting early oxidative injury, predicting disease trajectory, and differentiating reversible from progressive forms of renal impairment. These biomarkers include those derived from oxidative stress pathways, mitochondrial damage, inflammation, tubular epithelial injury, and epigenetic modifications. This review synthesizes emerging evidence on mechanisms linking redox dysregulation to the transition from acute kidney injury to chronic kidney disease and highlights the most promising biomarkers for early diagnosis, risk stratification, and therapeutic monitoring. Understanding these mechanistic and diagnostic breakthroughs is crucial for guiding targeted interventions aimed at preventing kidney disease progression.

Keywords: Acute kidney injury, chronic kidney disease, oxidative stress, redox imbalance, biomarkers

INTRODUCTION

Acute kidney injury is a multifactorial syndrome characterized by a rapid decline in renal function due to ischemia, toxins, sepsis, or drug exposure [1]. While many patients recover kidney function, a substantial proportion progress to chronic kidney disease, defined by persistent reductions in glomerular filtration rate, structural damage, or altered renal biomarker profiles. This transition is not a linear process but rather a continuum influenced by the severity of the initial insult, the adaptive capacity of renal tissue, systemic health conditions, and molecular determinants such as oxidative stress and mitochondrial dysfunction [2,3]. Redox imbalance is increasingly recognized as a unifying mechanism in nephrotoxicity and AKI progression. Reactive oxygen species are essential signaling molecules under normal physiological conditions, but their overproduction or impaired clearance leads to lipid peroxidation, protein oxidation, DNA damage, and cellular death [4]. These alterations promote maladaptive repair characterized by fibrosis, tubular atrophy, chronic inflammation, and vascular rarefaction, all hallmarks of CKD. Traditional biomarkers such as serum creatinine and urea nitrogen lack sensitivity for early detection of renal injury and provide limited insight into underlying molecular events [5]. The urgent need for earlier and mechanistically relevant biomarkers has catalyzed research into oxidative stress indicators, mitochondrial-derived molecules, inflammatory mediators, and epigenetic signatures [6]. These novel biomarkers hold promise not only for diagnosis but also for predicting patient outcomes and guiding therapeutic interventions designed to disrupt the AKI-to-CKD continuum.

2. Mechanisms of Renal Toxicity and Redox Imbalance

Toxicant-induced kidney injury is mediated through a combination of direct tubular cell damage, endothelial dysfunction, immune activation, and profound disturbances in redox regulation [7]. The kidney's high metabolic activity, dense mitochondrial content, and extensive microvascular network make it uniquely vulnerable to toxicants such as heavy metals, pharmaceuticals, industrial chemicals, and endogenous metabolic by-products [8]. Although these toxicants differ in chemical properties and modes of entry, they converge on pathways that elevate reactive

oxygen and nitrogen species beyond the kidney's antioxidant capacity [9]. This imbalance drives structural and functional deterioration that can progress from acute injury to long-term renal impairment.

2.1 Mitochondrial Dysfunction

Mitochondria play a pivotal role in renal physiology by generating ATP required for solute transport, maintaining ionic gradients, and regulating cell survival pathways [10]. During nephrotoxic exposure, these organelles become both sources and targets of oxidative stress. Agents such as cisplatin, vancomycin, aminoglycosides, amphotericin B, and radiocontrast media impair complexes I, III, and IV of the electron transport chain [11]. This impairment causes electrons to prematurely react with oxygen, generating excess superoxide. Mitochondrial membranes become increasingly permeable as lipid peroxidation progresses, leading to dissipation of the membrane potential, defective ATP synthesis, and opening of the permeability transition pore [12]. These events culminate in the release of cytochrome c, apoptosis-inducing factor, and mitochondrial DNA into the cytoplasm. Mitochondrial DNA is a potent danger signal capable of activating pattern recognition receptors and triggering inflammatory cascades [13]. Prolonged mitochondrial injury severely compromises the energetic viability of tubular cells, promoting apoptosis and necrosis that manifest clinically as acute kidney injury.

2.2 Oxidative Stress and Antioxidant Depletion

Accumulation of reactive oxygen species leads to extensive oxidative modification of cellular macromolecules. Polyunsaturated fatty acids within membranes undergo peroxidation, thereby compromising membrane integrity, altering ion transport, and generating toxic secondary aldehydes such as malondialdehyde and 4-hydroxynonenal [14,15]. These aldehydes form adducts with proteins and DNA, impairing enzymatic functions and contributing to mutagenesis. Antioxidant defenses become rapidly overwhelmed. Glutathione is depleted through conjugation with toxic metabolites, while enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase are inhibited or degraded under persistent oxidative pressure [16]. Loss of these systems increases vulnerability to further ROS accumulation, establishing a cycle of oxidative stress that reinforces tissue injury.

2.3 Inflammation and Immune Activation

Oxidative stress and cellular damage trigger inflammatory signaling pathways that recruit immune cells to the site of injury. Activation of NF-kB and AP-1 promotes transcription of cytokines such as TNF alpha, IL-1 beta, and IL-6 [17]. Endothelial and tubular cells upregulate adhesion molecules, facilitating leukocyte infiltration. Recruited macrophages and neutrophils produce additional ROS through NADPH oxidase, amplifying the oxidative burden. This inflammatory response initially serves to clear damaged cells but becomes detrimental when excessive or unresolved [18]. Chronic inflammation induces fibroblast activation, extracellular matrix deposition, and structural remodeling that drive long-term kidney dysfunction.

2.4 Endothelial Dysfunction and Microvascular Injury

The renal microvasculature is highly sensitive to redox disturbances. Toxicants impair endothelial nitric oxide synthase, reducing nitric oxide production and altering vascular tone [19]. Superoxide reacts with residual nitric oxide to form peroxynitrite, a reactive nitrogen species that damages endothelial proteins, lipids, and DNA. Peroxynitrite also promotes endothelial apoptosis, leading to capillary rarefaction. Loss of peritubular capillaries diminishes oxygen delivery to tubular cells, creating regions of chronic hypoxia [20]. Hypoxic stress activates pathways that further stimulate inflammation and fibrosis, reinforcing the transition from acute to chronic kidney pathology.

2.5 Maladaptive Repair and Fibrogenesis

While the kidney possesses significant regenerative capacity, severe or repeated oxidative injury disrupts the normal repair process. Instead of proliferating and differentiating, damaged tubular epithelial cells may enter a senescent state or undergo partial epithelial-to-mesenchymal transition [21]. These cells fail to restore functional nephron architecture and instead secrete profibrotic cytokines such as transforming growth factor beta and connective tissue growth factor. Activated fibroblasts and myofibroblasts accumulate in the interstitium, producing excessive collagen and extracellular matrix components [22]. This maladaptive repair forms the core mechanistic link between acute injury and progressive renal fibrosis, a defining feature of chronic kidney disease.

3. Transition From Acute Kidney Injury to Chronic Kidney Disease

The evolution from acute kidney injury to chronic kidney disease represents a dynamic continuum rather than two distinct clinical events [23]. While many patients recover renal function after an acute insult, a significant proportion develop long-term impairment driven by persistent redox imbalance, chronic inflammation, and structural remodeling [23]. Understanding the processes underlying this transition is essential for the development of targeted diagnostic and therapeutic approaches.

3.1 Persistent Oxidative Stress

Even after clinical indicators of AKI normalize, subclinical oxidative stress may continue within surviving tubular epithelial cells. Damaged mitochondria remain dysfunctional and produce elevated levels of ROS for weeks or months following the initial injury [24]. Persistent oxidative stress maintains inflammatory signaling, promotes

extracellular matrix deposition, and accelerates apoptotic and necrotic processes that cumulatively reduce renal reserve [25].

3.2 Tubular Epithelial Cell Senescence

Cellular senescence is a key determinant of maladaptive repair. Senescent tubular cells exhibit growth arrest and secrete a suite of inflammatory and fibrogenic mediators collectively known as the senescence-associated secretory phenotype [26]. Redox imbalance is a strong inducer of senescence, as oxidative damage to DNA and organelles activates the p53 and p21 pathways. Senescent cells resist apoptosis and persist long term, creating a microenvironment conducive to fibrosis [27]. Their presence correlates strongly with future decline in glomerular filtration rate.

3.3 Loss of Microvascular Integrity

Microvascular rarefaction following AKI leads to sustained renal hypoxia, a powerful driver of CKD progression [28]. Loss of endothelial cells disrupts nutrient and oxygen delivery to tubular segments, causing ongoing mitochondrial stress and ROS production. Hypoxia-inducible factor signaling becomes chronically activated, promoting fibrogenesis and impairing tubular regeneration [29,30]. Persistent microvascular injury predicts long-term functional decline more reliably than initial creatinine levels.

3.4 Immune Dysregulation

Innate and adaptive immune responses, once activated during AKI, may fail to resolve fully. Macrophages shift from clearing debris to promoting fibrosis through secretion of TGF beta and matrix-modifying enzymes [31]. Redox perturbations maintain this pro-fibrotic phenotype by altering transcriptional and metabolic programming. Similarly, T cell subsets may become dysregulated, contributing to chronic inflammation and tissue remodeling [32]. Persistent immune activation is a hallmark of the AKI-to-CKD transition.

3.5 Epigenetic Reprogramming

Oxidative stress induces long-lasting epigenetic changes that lock renal cells into maladaptive states [33]. DNA methylation patterns shift toward suppression of genes involved in cellular repair and antioxidant defense, while histone modifications promote expression of inflammatory and fibrogenic pathways [34]. MicroRNAs further modulate gene expression programs by suppressing mRNAs involved in mitochondrial function, endothelial repair, and epithelial regeneration. These epigenetic alterations create a form of molecular memory that maintains chronic disease processes even after the initial insult has resolved [35].

CONCLUSION

Redox imbalance represents a pivotal mechanism driving the transition from acute kidney injury to chronic kidney disease, linking cellular damage, mitochondrial dysfunction, inflammation, and maladaptive repair. The identification of novel biomarkers reflecting oxidative stress, mitochondrial injury, tubular epithelial damage, and epigenetic reprogramming has revolutionized our ability to detect renal injury at an early stage, often before conventional clinical markers rise. These biomarkers not only improve risk stratification and prognosis but also guide the development and monitoring of targeted therapies aimed at restoring redox homeostasis and preventing fibrosis. Integrating molecular biomarker data with imaging, clinical parameters, and personalized patient profiling promises to enhance precision nephrology, enabling timely intervention, reducing CKD progression, and ultimately decreasing the long-term global burden of kidney disease.

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