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The Role of Oxidative-Antioxidative Stress and Uromodulin Indicators and Polymorphism of Its Genes in the Development of Cardiorenal Syndrome

Khalilova Feruza Abdujalolovna
Associate Professor, Department of Propaedeutics of Internal Diseases, Bukhara State, Medical Institute, PhD

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Annotation: Cardiorenal syndrome (CRS) associated with chronic heart failure (CHF) is characterized by simultaneous impairment of cardiac and renal function, leading to increased complications and decreased quality of life in patients. Oxidative stress is an imbalance in the antioxidant system, associated with inflammatory processes, including malondialdehyde (MDA), superoxide dismutase (SOD), and α-tumor necrosis factor (α-TNF), which aggravates the course of CRS. In particular, the effect of uromodulin indicators and polymorphism of its genes on these processes is one of the important areas that are not well covered from a scientific and practical point of view.

Uromodulin (Tamm-Horsfall protein) is an important glycoprotein in the kidney, and its secretion and genetic characteristics can directly affect kidney function, inflammation, and oxidative stress processes. Therefore, the study of uromodulin indicators and its gene polymorphisms in the development of CRS is undoubtedly important for the diagnosis of CRS, individualization of treatment and improvement of nutritional status.

Keywords: uromodulin, cardiorenal syndrome, malondialdehyde (MDA), superoxide

dismutase (SOD), α-tumor necrosis factor (α-O'NO).

The process of ischemia/reperfusion in the kidney triggers a systemic inflammatory cascade, which leads to increased synthesis of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), further aggravating kidney damage. Inflammatory factors are associated with heart failure and contribute to cardiac hypertrophy through multiple pathways, including activation of nuclear factor kappa β (NF-κβ). In addition to inflammation, an imbalance between antioxidants and oxidants is observed in both organs, the heart and the kidney, after ischemia/reperfusion. This imbalance in favor of oxidants leads to the accumulation of certain reactive oxygen species (ROS), which can lead to cell damage.

This process is called oxidative stress and plays an important role in a number of cellular signaling pathways that damage proteins, lipids, and DNA, ultimately leading to cell apoptosis. A number of enzymes function to prevent the accumulation of PFAS and/or to attenuate the effects of PFAS. Enzymes such as catalase and superoxide dismutase (SOD) lead to the dismutation of superoxide anion (O2−) and the subsequent decomposition of hydrogen peroxide (H2O2) and hydroperoxides into water, alcohol, and oxygen. SOD has been found to play an important role in the regulation and protection of kidney damage and blood flow. On the other hand, several CSF production mechanisms that are required at basal level act as antioxidant balance For example, O2− is catalyzed by the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) and can react with nitric oxide (NO) at nearly diffusion rates to form peroxynitrite (ONOO−). This suggests that ischemia/reperfusion injury affects several aspects of the kidney. The consequences of damage by CSF at various levels in the body are directly related to many pathologies, demonstrating the biological importance of redox regulation. It is known that the pathogenesis of kidney damage may be associated with tissue NO deficiency. NO, produced by the constitutive isoform of NO synthase (NOS), performs a number of protective functions.

However, NO produced by inducible NOS (iNOS) is detrimental during ischemia/reperfusion. Therefore, in the kidney, a decrease in the amount of NO produced by endothelial NOS (eNOS) and a subsequent increase in the amount produced by iNOS are associated with inflammation and vasoconstriction during the early stages of reperfusion. As observed in this study, the modulation can occur at different times of reperfusion, increasing hours after ischemia in response to injury and increasing again several weeks later in response to increased inflammatory cytokines and organ atrophy at day 8. Once formed, NO can be converted mainly to NO2−, nitrate (NO3−), and S-nitrosothiol (RSNO), which act as both oxidizing and antioxidant agents. Several studies have demonstrated the role of NO2− as a potent mediator of cytoprotection in ischemia/reperfusion models by inhibiting mitochondrial complex I activity and reducing mitochondrial CPP formation after ischemia. During ischemia is limited by a decrease in NOS synthesis, NO2− is likely to be the main source of non-NOS-dependent NO production in the organ. Given this, Wellington Caio-Silva and coauthors expected that the bioavailability of NO in the kidney would decrease in a model of depletion of the reserve. It is possible that the observed modulation of renal NO2− and RSNO may be related to an increase in NOS activity before the analyzed times.

Summary:

Nephroprotection in patients with CJD requires a multi-step and cellular approach. Uromodulin early biomarkers allow for the early detection of CJD. Current evidence suggests that when these advances are put into practice, the rate of hCFT growth slows in patients and hospital admissions are reduced by 20–35%. At the same time, advances in genomics and proteomics are expected to soon bring new targets (e.g., NOX-4 inhibitors) to patients.

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