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Oxidative stress and hypoxia parameters in children with nephrotic syndrome

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Abstract. Nephrotic syndrome (NS) is a kidney disorder caused by increased permeability of the glomerular filtration barrier. The diagnosis is based on four main clinical features: edema, hyperlipidemia, hypoalbuminemia, and proteinuria. The pathogenesis of NS is linked to multiple pathways, including inflammation and apoptosis. The present study aimed to assess oxidative stress and hypoxia parameters in children with NS.

Methods. This cross-sectional study included 88 patients with NS at different stages of chronic kidney disease (CKD) and 25 healthy individuals (control group). Plasma samples were used to measure intracellular hypoxia-inducible factor alpha (HIF-1 α) and manganese superoxide dismutase (Mn-SOD). The levels of superoxide radicals were assessed using the electron paramagnetic resonance (EPR) method. ANOVA, followed by the post hoc Kruskal-Wallis test for multiple comparisons, was used to determine statistical significance. Statistical analysis was performed using Past4 software for Windows. A p -value <0.05 was considered statistically significant.

Results. A significant increase in the generation rate of superoxide radical anions ($O_2^{\cdot-}$) by neutrophils was detected in all children with NS (1.55 ± 0.7 nmol/ 1×10^3 cells/min in the CKD I stage group and 2.79 ± 0.22 nmol/ 1×10^3 cells/min in the CKD II–III stage group, $p < 0.01$). The expression of Mn-SOD was reduced to $76.57 \pm 4.62\%$ in the CKD I stage group and further decreased to $59.03 \pm 3.23\%$ in the CKD II–III stage group, compared to the control group ($p < 0.01$ and $p < 0.001$, respectively). Individual analysis of plasma HIF-1 α levels and Mn-SOD levels revealed a significant inverse correlation between these biomarkers ($r = -0.71$, $p < 0.0001$, CI: -0.8003 to -0.5878).

Conclusions. This study demonstrates that oxidative stress activation leads to a significant reduction in antioxidative capacity in children with nephrotic syndrome. An inverse correlation was observed between Mn-SOD levels and plasma HIF-1 α levels, suggesting a potential interplay between oxidative stress and hypoxia in NS pathogenesis.

Key words: oxidative stress, anti-oxidative defense, hypoxia, nephrotic syndrome, children.

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Показники окисного стресу та гіпоксії у дітей з нефротичним синдромом

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Резюме. Нефротичний синдром (НС) є захворюванням нирок, яке виникає в результаті підвищення проникності клубочкового фільтраційного бар'єру. набряки, гіперліпідемія, гіпоальбумінемія та протеїнурія є чотирма основними клінічними ознаками, які використовуються для встановлення діагнозу. Патогенез НС пов'язаний з кількома шляхами, включаючи запалення, апоптоз, тощо. Метою цього дослідження було вивчення показників окислативного стресу та гіпоксії у дітей з НС.

Методи. Проведено одномоментне дослідження, в яке включено 88 пацієнтів з НС з різною стадією хронічної хвороби нирок (ХХН) та 25 здорових дітей (контрольна група). Зразки плазми використовували для вимірювання маркера внутрішньоклітинної гіпоксії, - гіпоксія-індукованого фактора 1-альфа (HIF-1 α) та антиоксидантного маркера манганцевої супероксиддисмутази (Mn-SOD). Метод електронного парамагнітного резонансу (ЕПР), використаний для вимірювання рівнів супероксидних радикалів. ANOVA з тестом Краскела-Уолліса для порівняння незалежних змінних, застосовано для перевірки значущості відмінностей. Програмне забезпечення Past4 для Windows використано для статистичної обробки даних. Значення $P < 0,05$ вважаються статистично значущими.

Результати. Значне прискорення швидкості генерації супероксидних радикалів (O₂⁻) нейтрофілами, виявлено в усіх дітей із НС (1.55 ± 0.7 нмоль/л·10³ клітин·хв у групі ХХН I стадії та 2.79 ± 0.22 нмоль/л·10³ клітин·хв у групі з ХХН II-III стадії, $p < 0.01$). Експресія Mn-SOD знизилася до $76.57 \pm 4.62\%$ порівняно з контролем у групі ХХН I стадії та до $59.03 \pm 3.23\%$ у групі з ХХН II-III стадії ($p < 0.01$ та $p < 0.001$ відповідно, порівняно з групою контролю). Індивідуальний аналіз рівня HIF-1 в плазмі крові та рівня антиоксидантного ферменту Mn-SOD у виявив наявність негативної кореляції між цими біомаркерами ($r = -0.71$, $p < 0.0001$, ДІ: від -0.8003 до -0.5878).

Висновки. Було показано, що фоновий стан, пов'язаний з активацією окислативного стресу, викликає значну втрату антиоксидантної здатності у дітей з нефротичним синдромом. Індивідуальний аналіз показників виявив зворотний негативний кореляційний зв'язок між рівнями антиоксидантного ферменту Mn-SOD і HIF-1.

Ключові слова: окислативний стрес, антиоксидантний захист, гіпоксія, нефротичний синдром, діти.

Introduction. Heavy proteinuria, hypoalbuminemia, hyperlipidemia, and edema are caused by the glomerular filtration barrier's enhanced permeability in nephrotic syndrome. It has been reported that there are two to seven instances per 100,000 children, mainly affecting the pediatric population [1]. Inflammation and oxidative stress have been linked to the pathophysiology and consequences of neuropathy, even though the condition is frequently idiopathic in juvenile patients [1, 2]. The majority of individuals with idiopathic NS experience clinical remission after 4 weeks of therapy with glucocorticoids. No matter how long they have been exposed to glucocorticoids or whether they are in remission, children with NS have more cardiovascular risk factors than other pediatric patients [1, 3].

Hypoxia in those kids is associated with inflammation and oxidative damage. Reactive oxygen species (ROS) and the antioxidant system that neutralizes them are out of balance in an oxidative stress state, which impairs cellular signaling and causes cell damage [4]. By weakening the glomerular filtration barrier, encouraging inflammation, changing lipid metabolism, compromising endothelial function, and inducing cellular damage, oxidative stress can play a role in the onset and progression of NS [5]. Numerous investigations have demonstrated that NS patients have significant levels of oxidative stress during the acute stage of the illness, and other research has found that oxidative stress indicators are elevated even after the disease has responded to steroid treatment [6–8].

Despite their resource-intensive and time-consuming nature as well as their limitations in capturing the combined prooxidant and antioxidant impact, previous NS research predominantly assessed individual prooxidant and antioxidant indicators [2, 8, 9]. Previous research mostly concentrated on lipid peroxidation in NS, particularly malondialdehyde (MDA) [8, 9].

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Evaluation of both damaged stable molecules and antioxidant molecules, including enzymatic and non-enzymatic antioxidants, is required for the assessment of oxidative stress.

This study's goal is to assess the parameters of hypoxia and oxidative stress status in kids with hormone-sensitive forms of NS to look for any potential correlations between them.

Material and methods. Patients. This cross-sectional study was carried out on 88 children with nephrotic syndrome. Informed written consent was obtained from the parents of all participants. The study was approved by the local ethical committee of the Medical University and the research complied with the Helsinki Declaration. The inclusion criteria were as follows: children with steroid-sensitive nephrotic syndrome (SSNS) (proteinuria >3 gm/day, hypoalbuminemia, and edema; patients who were informed and agreed to participate in this study. The exclusion criteria were the following: patients with steroid-resistant forms of NS; patients with missing clinical data, patients with other proteinuric diseases; and patients with concomitant inflammatory, autoimmune diseases, cancer, diabetes, and allergy. The steroid-sensitive nephrotic syndrome (SSNS) group were those who responded to steroid treatment within 8 weeks. The control group consists of 25 healthy individuals. We used an online calculator to determine body mass index (BMI) from weight (kg) and height (cm) for children. Blood pressure measurement was measured in a sitting position by using a mercury sphygmomanometer with an appropriate cuff size. The glomerular filtration rate (GFR) was evaluated using the online calculator.

Immunoblotting for detection of HIF-1 α . Plasma samples were used to measure marker intracellular hypoxia HIF-1 α and Mn-SOD. Proteins solubilized in Laemmli sample buffer were resolved in polyacrylamide gels by SDS-PAGE and transferred to a polyvinylidene difluoride membrane. Membranes were then blocked in 5% non-fat milk in TBS-T (136 mM NaCl, 10 mM Tris, 0.05% Tween 20) and immunoblotted using the HIF-1 α Ab (Cell Signaling Technology, Danvers, MA USA) for 1 hour at room temperature. The actin mouse mAb was used as a loading control. After three washes with TBS-T, the membranes were incubated with secondary anti-rabbit or anti-mouse antibodies labeled with horseradish peroxidase for 1 hour at room temperature. Membranes were washed three times with TBS-T. The protein bands were visualized by chemiluminescent substrate ECL. Quantification of the protein content was done by densitometric analysis.

Superoxide detection. The method of determining the rate of the superoxide generation is carried out as follows. Neutrophils are isolated from 2 ml of venous blood of the studied patients with 3% trilon B according to a known method. The resulting cells used to measure the generation of superoxide radical anions using the spin trap 1-hydroxy-2,2,6,6-tetramethyl-4-oxopiperidine hydrochloride (TEMPONE-H) and the

method electron paramagnetic resonance (EPR) in a special paramagnetically clean quartz cuvette at room temperature.

Statistics. The data is expressed as means \pm SEM and as frequencies and percentages when appropriate. ANOVA followed by the post hoc Kruskal-Wallis test for multiple comparisons used to test the significance of differences. Pearson correlation was run to study the correlation between factors. The sample size was calculated by online calculator. The power equaled 0.9 used in this study. Data processed using Past4 Software for Windows (USA). P values <0,05 are considered statistically significant.

Results. Patients. The main causes of NS in the examined children were glomerulopathies (focal segmental glomerulosclerosis, membranous glomerulonephritis) – 92%, IgA nephropathy – 5%, rapidly progressive glomerulonephritis – 3%. Examination of children with NS included general clinical examination; complete blood count; urinalysis; daily proteinuria measurement; blood glucose test; biochemical parameters measurement – blood protein, Serum creatinine and urea, blood serum cholesterol; instrumental examination - electrocardiography (ECG), ultrasound examination of abdominal organs and kidneys (USD), daily blood pressure monitoring.

The average age of patients is 12.25 \pm 0.85 years, and the average duration of the disease is 7.65 \pm 0.33 years. 55.3% of the patients included in the study were boys and 44.7% were girls. The average value of BMI was 21.8 \pm 0.73. Values of heart rate and blood pressure were measured at the reception before inclusion in the study. The heart rate value was 84.67 \pm 3.02 bpm. Systolic blood pressure in the group was 126.5 \pm 2.44 mmHg, diastolic blood pressure was 81.22 \pm 1.08 mmHg. Edema was detected in all examined subjects, and hypertension in 48.6%.

All patients underwent a complete blood count test. Indicators of erythrocytes, leukocytes, platelets, Hb, and ESR were analyzed. Erythrocytes number was 4.02 \pm 0.3 \cdot 10¹²/l, leukocytes 8.37 \pm 0.65 \cdot 10⁹/l, platelets 297.6 \pm 8.64 \cdot 10⁹/l, hemoglobin – 118.2 \pm 1.62 g/l, ESR – 13.8 \pm 1.13 mm/h.

The main biochemical indicators of all children with NS were evaluated. Proteinuria level, GFR, and serum creatinine level were selected as indicators for kidney function assessment. The average level of proteinuria was 8.12 \pm 0.8 g/24 h, GFR - 95.4 \pm 4.04 ml/min/1.73 m², serum creatinine 70.23 \pm 2.38 μ mol/l. The level of cholesterol in the blood serum as a marker of lipid metabolism disorders was recorded at the level of 10.24 \pm 1.33 mmol/l, total blood protein 49.17 \pm 1.5 g/l, blood alpha2 globulins 25.57 \pm 0.3 g/l.

In the course of the study, it was established that the main complaints of patients with NS were: edema - in 88 (100%) of the examined, headaches - in 67 (76.1%) patients, lack of appetite - in 61 (68.9%), thirst – in 69 (78.9%) examinees (Fig. 1).

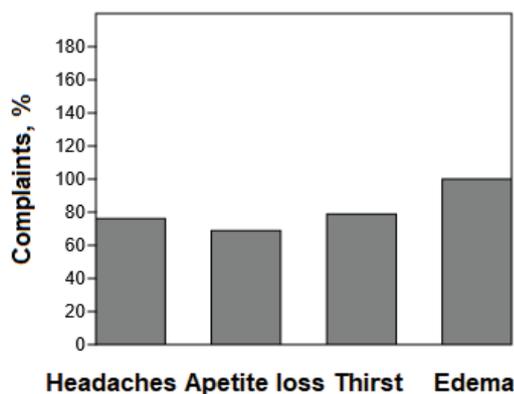


Fig. 1. Complaints in examined children with nephrotic syndrome.

Markers of oxidative stress in nephrotic children. A study of the levels of activation of blood neutrophils in children with NS revealed a significant acceleration of the rate of generation of superoxide radical anions (O_2^-), characteristic of chronic inflammation (Fig. 2).

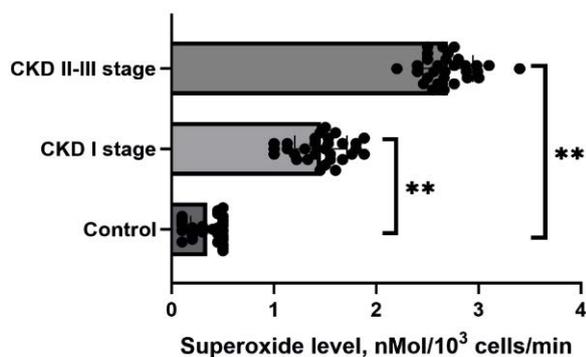


Fig. 2. Levels of inflammatory activation of blood neutrophil granulocytes in children with NS and controls depending on the CKD stage. Note: ** – $p < 0.01$ – statistically significant level.

At the same time, the degree of inflammatory activation of cells depended on the presence of a violation of the filtering function of the kidneys - more pronounced changes were recorded in patients with a slowing of the rate of GFR in CKD II-III stage (2.79 ± 0.22 nmol/1·10³ cells·min versus 1.55 ± 0.7 nmol/1·10³ cells·min in the group with CKD I stage, $p < 0.01$).

Oxidative stress is an important pathogenetic component in the development of inflammation in kidney pathologies that have a chronic course. Oxidative stress develops as a result of an imbalance between the level of production of radical forms of oxygen and the state of activity of antioxidant protection. The development of oxidative stress is the primary disturbance in the occurrence of the following. The following signaling reactions are associated with the activation of cellular signaling, which triggers cell apoptosis, a decrease in their regenerative capacity, and fibrosis. These factors have a stochastic damaging effect on kidney function.

ROSs are very destructive molecules for cells. At the same time, these ROSs play an important physiological role in kidney physiology, acting as activators in signaling pathways. However, even with their formation

in the processes of normal mitochondrial respiration, RFK can accumulate excessively, which ultimately leads to the loss of positive aspects of their cellular and tissue functions and, ultimately, to the development of a pathological process.

The kidney is a highly functional organ, the functioning of which relies heavily on aerobic metabolism for the production of ATP by oxidative phosphorylation. Recovery of molecular O_2 in the mitochondrial respiratory chain is vital for kidney cell function, but potentially disruptive in the long term. The mitochondrial respiratory chain consists of five multi-enzyme complexes, which are responsible for maintaining mitochondrial membrane potential and ATP synthesis. Each of these complexes is a ROS generation site; however, the main ones are complexes I and III, which are defined as the main O_2 sites of generation. Damage to respiratory complexes and substrates leads to ineffective electron transfer, and the subsequent increase in ROS synthesis, decrease in ATP synthesis, and loss of mitochondrial membrane potential. The above-described processes take place in diseases that are associated with chronic inflammation, which is accompanied by the activation of oxidative stress.

The state of antioxidant protection in children with nephrotic syndrome. The levels of Mn-SOD were analyzed in all patients. A decrease in the level of antioxidant protection was found in all children with NS. At the same time, the degree of inhibition of antioxidant protection in NS depends on the presence of impaired kidney function. Thus, with preserved function (CKD I stage), the expression of Mn-SOD was reduced to $76.57 \pm 4.62\%$, compared to the control. With a more prominent decrease in GFR (CKD II-III stage), a decrease in the level of the indicator was observed down to $59.03 \pm 3.23\%$ ($p < 0.01$ and $p < 0.001$, respectively, compared to the control group) (Fig. 3).

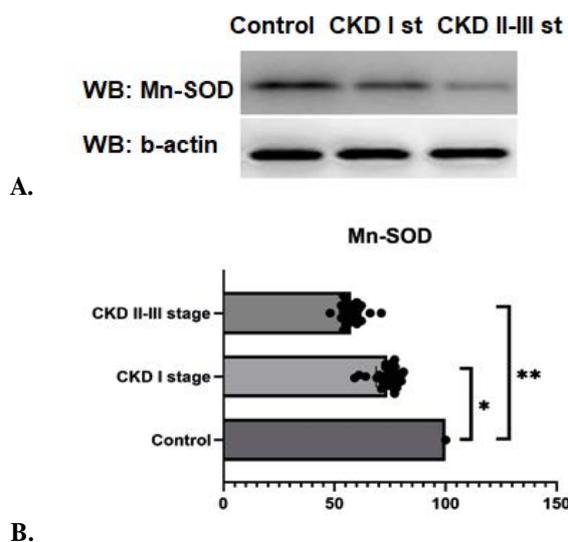


Fig. 3. (A) Western blot of the antioxidant biomarker Mn-SOD in children with NS and various stages of CKD. (B) Indicators of Mn-SOD levels in children with NS and various stages of CKD. * – $p < 0.05$, ** – $p < 0.01$ – statistically significant levels. WB – Western Blotting.

Individual analysis of the level of HIF-1 α plasma and the level of the antioxidant enzyme Mn-SOD in patients determined the presence of an inverse negative correlation ($r=-0.71$, $p<0.0001$, CI: -0.8003 to -0.5878) (Fig. 4). These data indicate the dependence of the level of chronic hypoxia on the degree of damage to the filtration barrier of the kidneys and confirm the direct involvement of hypoxic damage in the progression of NS.

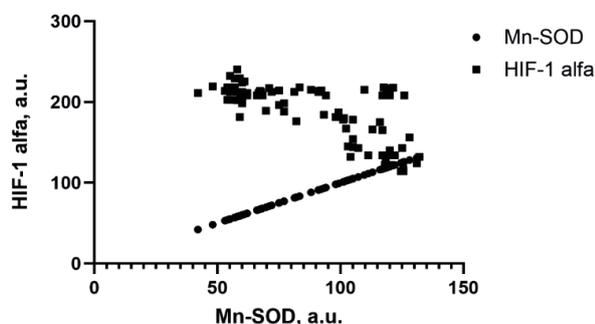


Fig. 4. The relationship between the plasma HIF-1 α level and the antioxidant enzyme Mn-SOD in children with nephrotic syndrome.

Discussion. The inflammation underlying the pathogenesis of NS is manifested both in the form of an isolated local inflammatory reaction and as part of a systemic inflammatory disorder that leads to interstitial fibrosis, tubular atrophy, and glomerulosclerosis [2-4].

Cellular reactions that take part in the implementation of this inflammation include activation, migration, and adhesion of pro-inflammatory cells (neutrophils, monocytes/macrophages, lymphocytes) with the implementation of a wide range of inflammatory mediators, including adhesion molecules, proteases, enzymes, oxygen free radicals, chemokines, growth factors, pro- and anti-inflammatory cytokines [10]. We have previously shown that pediatric patients with NS have high levels of hypoxia and this parameter gradually progresses with decreased kidney function [11, 12].

Numerous diseases have been linked to oxidative stress, which is an imbalance between the body's antioxidant defenses and the creation of ROS. Numerous illnesses, such as autoimmune disorders, metabolic diseases, and cardiovascular pathologies, demonstrate the significant influence of oxidative stress on cellular homeostasis and tissue integrity. Disturbance of redox balance is a major factor in the initiation of inflammatory reactions and exacerbation of various medical disorders, including rheumatoid arthritis, diabetes mellitus, atherosclerosis, obesity, and hypertension [13].

Because hypoxia plays a major role in renal fibrosis, it may be possible to prevent or delay the illness by therapeutically modifying the hypoxic response. Hypoxia-inducible factors (HIFs), such as HIF-1 α and HIF-2 α , are the main agents that trigger the cellular hypoxic response [14].

Oxygen level has a specific impact on HIF-1 α stability, subcellular localization, and transcriptional activity. Hypoxia, on the other hand, prevents the HIF-

1 α protein from degrading and increases HIF-1 α levels, which then bind to HIF-1 β and activate target genes through transcription [15].

Oxidative stress and increased generation of reactive oxygen species (ROS) have also been linked to hypoxia [16]. ROS is a tool with two sides. Low ROS concentrations are crucial signaling molecules in a variety of pathological mechanisms. On the other hand, too much ROS causes cellular damage and starts the cell death process. HIF-1 is a heterodimer consisting of an O₂-regulated α subunit and a constitutively produced β subunit that plays a crucial role in cellular responses to hypoxia. α subunit levels are controlled by ubiquitin-dependent proteasomal degradation in a normoxic environment [14-16].

The production of ROS under physiological conditions is in balance with the activity of antioxidant systems, such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and glutathione (GSH). It is shown that the accumulation of oxidative damage occurs mainly due to a decrease in the level of endogenous antioxidants, in parallel with an increase in the production of ROS. Thus, adequate activity levels of the body's antioxidant systems are vitally important for normal cell function [13].

Mitochondria have their own system of antioxidants, such as mitochondrial manganese-SOD (Mn-SOD), and copper/zinc-SOD (Cu/Zn-SOD), which converts O₂⁻ into H₂O₂, which then decomposes into H₂O and O₂. GPX is also present in mitochondria [17].

Inflammation, and activation of ROS generation by mitochondrial, cytoplasmic, and extracellular sources leads to the development of oxidative stress [13]. Endogenous antioxidants, ensure the termination of the lipid peroxidation reaction in the phospholipid bilayer of cell membranes. ω -3 fatty acids displace arachidonic acid in the cell membrane and thereby reduce the formation of ROS, which are derivatives of arachidonic acid, thereby significantly reducing inflammation and subsequent fibrosis [13-17]. Significant consequences of oxidative stress in plasma proteins are called advanced oxidation protein products (AOPP), which cause glomerular podocyte dysfunction and proteinuria by stimulating the Wnt/b-catenin signaling pathway [8].

The levels of Mn-SOD were analyzed in all patients. A decrease in the level of antioxidant protection was found in all children with NS. Individual analysis of the level of HIF-1 α plasma and the level of the antioxidant enzyme Mn-SOD in patients determined the presence of an inverse negative correlation ($r=-0.71$, $p<0.0001$, CI: -0.8003 to -0.5878) (Fig. 4). These data indicate the dependence of the level of chronic hypoxia on the degree of damage to the filtration barrier of the kidneys and confirm the direct involvement of hypoxic damage in the progression of NS.

This study has certain limitations that must be presented. Our study was cross-sectional, at a single center with somewhat limitations in patients including a con-

trol group. Moreover, factors that potentially can affect oxidative stress, i.e. variability in steroid therapy or nutritional status, have not been presented in this study.

Conclusions. In children with NS a background condition dealing with the activation of oxidative stress, a pronounced decrease in anti-oxidative capacity has been studied. Individual analysis of the level of HIF-1 α plasma and the level of the antioxidant enzyme Mn-SOD in patients determined the presence of an inverse negative correlation. We suggest that monitoring of oxidative stress marker (superoxide), a marker of chronic hypoxia (HIF-1 α), and an antioxidative marker (Mn-SOD) in children with NS may have a potential clinical significance in terms of further distinguishing groups for the additional therapeutic interventions.

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