Research Article

Imbalance in the oxidative stress system – antioxidant protection in patients with chronic pyelonephritis depending on the course of the disease

Olga A. Efremova*, Lyudmila A. Kamyshnikova, Suleiman E. Veysalov, Maria S. Sviridova, Natalya I. Obolonkova, Andrei A. Maslennikov, Maryam Wuraola

ABSTRACT

Objectives: Assessment of the imbalance in the system of oxidative stress (OS) – antioxidant protection in patients with chronic pyelonephritis (CP) depending on the course of the disease. **Materials and Methods:** Patients were divided into three groups: The first group (29 patients) consisted of patients with a recurrent course of CP, exacerbations of 3 or more times per year course of pyelonephritis (CPr); the second (34 patients) – patients with active phase of pyelonephritis (CPc), having comorbid cardiovascular pathology (stable coronary heart disease with heart failure I-II FC); and the third control group (35 patients) consisted of patients with an active phase of the disease (CP) who has had a history of pyelonephritis for at least 5 years, rare exacerbations – not more than once in a year. **Results:** It was established that patients with a recurring CPr, an increase in OS activity and an increase in malondialdehyde (MDA) production are characteristic against the background of a decrease in antioxidant protection parameters (AOP); moreover, the recurrent course of CP produced a more significant effect on patients: For patients with CPr (with 3 or more relapses per year) were characterized by lower superoxide dismutase (SOD) and catalase (CAT) values compared with similar indicators in the group of patients with CP without relapse. For patients with CP and comorbid pathology, a disturbance in the oxidative balance was also characteristic, which was manifested by an increase in the average levels of MDA and diene conjugate (DC) in the blood serum (by 12.3% and 9.1%, respectively, $P < 0.001$) against the background of a decrease average values CAT content (by 18.2%, $P < 0.001$) and a pronounced tendency for a decrease in SOD. **Conclusion:** In comparison with the recurrent CPr in patients with comorbid pathology, OS was more pronounced, which was manifested in a significantly greater increase in lipid peroxidation and a decrease in AOP factors. Perhaps increased free radical activity is one of the factors involved in the pathogenesis of the inflammatory syndrome in patients with CP and comorbid pathology.

KEY WORDS: Antioxidant system, Comorbid pathology, Free radical activity, Lipid peroxidation, Oxidative stress, Pyelonephritis

INTRODUCTION

Free radical oxidation (FRO) plays an important role in the pathogenesis of many chronic diseases such as diabetes mellitus, cancer, and chronic kidney disease (CKD).[1-4] Oxidative stress (OS) is defined as an imbalance in oxidizing agents and antioxidants, causing disruption of redox processes in cells.[5] Previous studies have shown that any inflammatory process, including in the kidney, leads to the initiation of FRO. Chronic pyelonephritis (CP) is a common and serious disease caused by a wide range of etiological factors.[6-8] In the pathogenesis of CP, OS plays an important role, the degree of the intracellular and extracellular OS is associated with the severity of kidney damage. Studies have shown that FRO is involved in progressive kidney damage.[9-12] The attack of FRO on polyunsaturated fatty acids with the initiation of lipid peroxidation (LPO) leads to changes in biological membranes and causes progressive damage to the kidneys. A group of endogenous and exogenous antioxidants representing the total antioxidant activity of extracellular fluids provides greater protection against FRO attacks.[3,13]

The connection between kidney disease and cardiovascular disease (CVD) has also been repeatedly proven and is expressed cardiorenal or renocardial

Access this article online

Website: jprsolutions.info | ISSN: 0975-7619

Department of Faculty Therapy, Belgorod State University, Medical Institute, Belgorod, Russia

Corresponding author: Olga A. Efremova, Department of Faculty Therapy, Belgorod State University, Medical Institute, Pobeda Street, 85, 308015 Belgorod, Russia. E-mail: efremova@bsu.edu.ru

Received on: 18-02-2020; Revised on: 21-03-2020; Accepted on: 27-04-2020

relationships.[14,15] OS is a common mediator linking CKD and CVD.[5,16] There are limited and conflicting data in the literature on the relationship between LPO and total antioxidant ability in patients with CKD and CVD.[14,16,17] Evaluation of OS in patients with various courses of CP and in case of comorbidity with cardiovascular pathology by measuring LPO and antioxidant system can lead to a better understanding of free radical damage in patients with CP.

The aim of the study is to assess the imbalance in the system of OS – antioxidant protection in patients with CP, depending on the course of the disease.

MATERIALS AND METHODS

A dynamic clinical, laboratory and instrumental examination of 62 patients with CP (CP) without symptoms of urinary tract obstruction was performed, which would require surgical intervention, aged 23–67 years, who were hospitalized and outpatient in the Nephrology Department of the Belgorod Regional Clinical Hospital. Among the examined, three groups were identified: The first group (29 patients) consisted of patients with a recurring course of CP, exacerbations of 3 or more times per year course of pyelonephritis (CPr); second (34 patients) – patients with an active phase of pyelonephritis (CPc), having comorbid cardiovascular pathology (stable coronary heart disease with chronic heart failure I – II FC); and the third control group (35 patients) consisted of patients with an inactive phase of the disease (CP) who had a history of pyelonephritis for at least 5 years, rare exacerbations – not more than 1 time per year. The groups were represented by age. Among the examined patients were 33 men and 63 women, i.e., the majority of patients with CP were women (64.3%). The duration of the disease was from 4 to 15 years, the average duration of CP was 8.7 ± 2.4 years. In 35 (35.7%) patients, CP was primary, in 64.3% – secondary, most often caused by urolithiasis, malformations, and position of the kidneys. The criteria for the diagnosis of CP were the presence of pain, intoxication, dysuria, urinary syndromes, and characteristic changes in excretory urograms and ultrasound of the kidneys. During the study, all patients underwent general clinical, biochemical, and instrumental examination methods. In addition, markers of OS were determined spectrophotometrically in blood serum:[1,18] The content of secondary products of LPO – malondialdehyde (MDA) and diene conjugate (DC). The activity of the antioxidant system was evaluated by the activity of superoxide dismutase (SOD) and catalase (CAT).

The results obtained were processed by methods of variation statistics using the computer program Statistica 6.0. The data are represented in the generally accepted form (M ± m), where M is the arithmetic mean error. Results were considered statistically significant, with an error probability of less than five percent (P<0.05).

RESULTS

The analysis of the content of LPO products in patients of all three groups was carried out [Table 1].

As presented in Table 1, the content of DC significantly differed in groups of patients. Hence, in patients with a recurring course of CP and pyelonephritis in combination with CVDs, the level of DC was significantly (P < 0.001) higher than in the control group (36.06 ± 1.21 and 39.35 ± 0.8 nmol/ml vs. 27.41 ± 1.53 nmol/ml, respectively). Moreover, in patients with CP and comorbid pathology, the content of DC with P < 0.001 was higher than in patients with CPr.

An increase in the content of reactive oxidants in the recurring CPr can be explained by several reasons: First, as a result of their formation under the constant influence of pro-inflammatory factors that forms complexes with various proteins, as well as due to the autoxidation of fatty acids in triglycerides, phospholipids, and cholesterol esters in the inflammatory process. Apart from this, additional factors that contribute to the formation of reactive oxidants in organs and tissues are ischemia and tissue hypoxia, which occurs during CP.[7,9,11,19]

The blood content of the examined patients of another lipid peroxidation (LPO) product – MDA – showed similar changes similar to DC: The value of the indicator in patients with CP, both during exacerbation and during remission, was significantly (P < 0.001) higher than in the control group. Moreover, the highest MDA level was in patients with CKD, which significantly (P < 0.001) distinguished the group with comorbid pathology from the control group (39.84 ± 1.6 and 32.12 ± 1.14 nmol/ml, respectively). In the first group, the MDA was also significantly higher (35.46 ± 1.21 nmol/ml) than the comparison group, P < 0.001.

MDA, by acting on platelet aggregation, promotes membrane destabilization and cell destruction, disrupts microcirculation and leads to the development of sclerotic processes in the kidneys.[5,16,20] Therefore, a significant increase in the concentration of MDA, along with an increase in the content of DC, confirms the increase in LPO in concomitant cardiovascular pathology in patients with pyelonephritis. Changes in these indicators and their severity, perhaps, are one of the links in the pathogenesis of the disease.[11,13,18,21]

The dependence of the LPO indices on the CPr is evidenced by the diagram shown in Figure 1.

The median of the DC index, which gives an idea of the concentration of lipid hydroperoxides, in the control group was 16.8 nmol/l, in the group of patients with

Table 1: Indicators of free radial blood oxidation of the examined patients

Indicators	1st group CPr, *n*=29	2nd group CPc, *n*=34	3rd group CP, *n*=35
DC, nmol/ml	36.06±1.21*	39.35±0.8**º	27.41±1.53
MDA, nmol/ml	35.46±1.21*	39.84±1.6**º	32.12±1.14

*Statistically significant differences between groups 1 and 3; ** – statistically significant differences between groups 2 and 3; – statistically significant differences between groups 1 and 2. CPr: Course of pyelonephritis, MDA: Malondialdehyde, DC: Diene conjugate

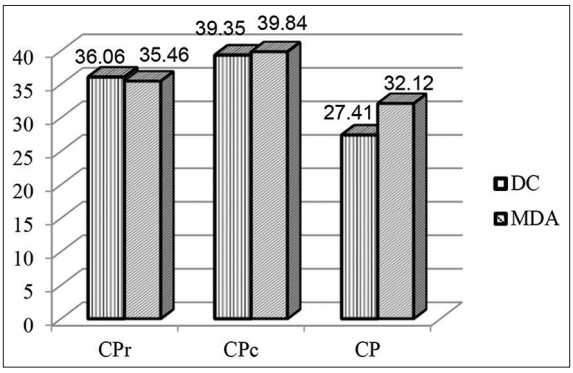

Figure 1: LPO indicators according to the study group

CKD it shifted to the level of 26.9 nmol/ml. In the group of patients with pyelonephritis and CVD, the value of the indicator was 37.4 nmol/L. Thus, the stage of CP exacerbation under conditions of comorbidity was accompanied by a further increase in the concentration of lipid hydroperoxides, which indicated the intensification of LPO processes. Dependence is statistically significant ($P < 0.05$, the Kruskal–Wallis test).

Free radicals are highly reactive, unstable chemical compounds that affect the vascular wall. It is possible that a significant increase in DC levels with increased free radical activity was found to be one of the factors involved in the pathogenesis of the inflammatory syndrome in patients with CP with comorbid pathology.

The end product of LPO is MDA, which inhibits prostacyclin and promotes platelet aggregation and thrombosis. Along with a decrease in prostacyclin synthesis, the level of thromboxane rises, which leads to the adherence of platelets to endothelial cells, disrupts microcirculation, initiates the atheromatous process, and promotes the formation of the atherosclerotic plaques.[20]

An important aspect is the study of the state of the antioxidant system in patients with CP. In our work, the state of the antioxidant system was evaluated by the content of SOD and CAT.

A comparison of the content of antioxidant defense (AOD) indicators of patients was performed in Table 2.

It was found that in patients with CP both in the recurrent course of the disease and in comorbidity, the SOD value was significantly ($P < 0.001$) lower than in the control group (43.24 ± 0.62 and 40.46 ± 0.99 against 46.31 ± 1.09 U/mg Hb min, respectively). At the same time, in patients with CKD, the content of SOD with $P < 0.001$ was than in patients with CPr [Figure 2].

Changes in SOD levels, the main role of which is the binding of reactive oxygen species with the formation of hydrogen peroxide, in patients with CP may be due to an increase in the accumulation of glyoxal and methylglyoxal in the plasma of patients.[11,12]

A similar disturbance was characteristic of another enzyme of the AOD system – CAT. In patients with a recurrent course of CP, the content of CAT was 0.121 ± 0.007 units/mg Hb min and was significantly ($P < 0.001$) lower than in the control group. In patients with a recurrent course of CP, it was 0.121 ± 0.007 units/mg Hb min and was significantly ($P < 0.001$) lower than in the control group. Furthermore, low values were in the group of patients with CKD, which significantly ($P < 0.001$) distinguished this group from the control (0.099 ± 0.008 and 0.143 ± 0.0066 units/mg Hb min, respectively) [Figure 3].

CAT is one of the main antioxidant enzymes; therefore, its decrease in patients with CP confirms a weakening of the antioxidant system activity and increases OS on the background of exacerbation of CP.

DISCUSSION

An analysis of the results showed that most patients with CP are characterized by an increase in the level of MDA against the background of a decrease in AOD, which contributes to the development of OS.

After analyzing the data obtained in the first and control groups, it was found that patients with a recurring CPr are characterized by an increase in OS activity and an increase in MDA production against the background of a decrease in AOD parameters; moreover, the recurrent course of CP produced a more significant effect on the changes in these parameters; patients with CPr (with 3 or more relapses per year) were characterized by lower values of SOD (7%) and CAT (by 18%) compared with similar indicators in the group of patients with CP without relapse.

For patients with comorbid pathology compared with the control group, the oxidative balance was generally disturbed, which was manifested by an increase in the average levels of MDA and DC in the blood serum (by 12.3% and 9.1%, respectively, $P < 0.001$) against the background of a decrease in the average indices of the

Table 2: Indicators of the antioxidant system in the blood of the examined patients

Indicators	1st group CPr, *n*=29	2nd group CPc, *n*=34	3rd group CP, *n*=35
SOD, u/mg Hb min	43.24±0.62*	40.46±0.99**º	46.31±1.09
CAT, u/mg Hb min	0.121±0.007*	0.099±0.008**º	0.143±0.006

*Statistically significant differences between groups 1 and 3; ** – statistically significant difference between groups 2 and 3; – statistically significant differences between groups 1 and 2. CPr: Course of pyelonephritis, SOD: Superoxide dismutase, CAT: Catalase

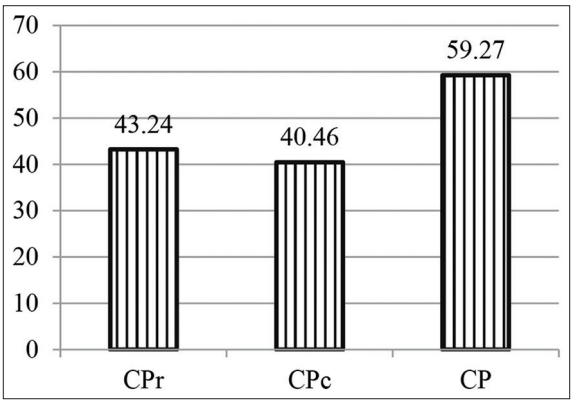

Figure 2: Superoxide dismutase level depending on the study group

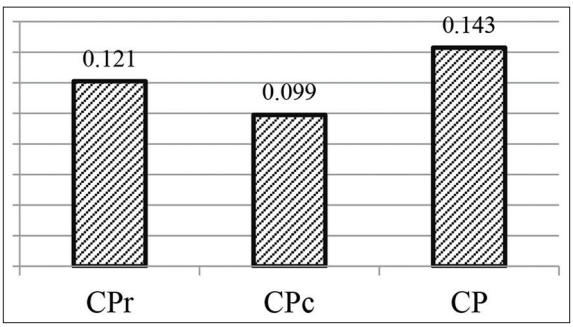

Figure 3: Catalase level depending on the study group

CAT content (by 18.2%, $P < 0.001$) and a pronounced tendency to a decrease in SOD [Table 2].

An increase in free radicals, in turn, contributes to the development of endothelial dysfunction with a disbalance in the ratio of vasoactive and vasoconstrictor substances to the predominance of vasoconstrictor mediators.[3,5,11,20] Vasoconstriction promotes the activation of pro-inflammatory factors and the maintenance of the inflammatory process in the kidneys. A vicious circle is forming, which is difficult to break, affecting only thee etiological factors leading to the development of CKD. As the results showed, the nature of the course of CP (recurrent or with comorbid pathology) undoubtedly affects the response of the LPO-AOD system. The antioxidant protection system (AOD) includes components of an enzymatic and non-enzymatic nature, which inhibit LPO both by neutralizing free radicals and by destroying hydroperoxides, which are also able to initiate this process. SOD catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide. Thus, it plays a crucial role in the AOD of almost all cells, which in one way or another are in contact with oxygen.

All these are consistent with modern ideas about the pathogenesis of pyelonephritis.[3,7,18,19] Thus, it is known that the formation of the process of infectious inflammation in the kidneys and urinary tract is associated with a "respiratory burst" in phagocytes and the creation of reactive oxygen species, which, by initiating oxidative processes, damage kidney tissue with the intensification of the destruction of biomembranes and activation of LPO.[12,21] It is also known that OS stimulates cell receptors that induce the production of pro-inflammatory cytokines and the expression of adhesion molecules. Hence, OS causes inflammation, which, in turn, again strengthens the OS. On this basis, a strategy to reduce the negative effects of OS and inflammation is one of the foundations for the treatment of CP, especially relapsing and associated pathology.

CONCLUSION

An analysis of the results showed that most patients with CP are characterized by an increase in MDA levels against a background of a decrease in AOD, which contributes to the development of OS. For patients with CP with comorbid pathology as a whole, a disturbance in the oxidative balance was observed, which was manifested by an increase in the average levels of MDA and DC in the blood serum (by 12.3% and 9.1%, respectively, $P < 0.001$) against a decrease in the average indicators of CAT content (by 18.2%, $P < 0.001$) and a pronounced tendency to a decrease in SOD. Compared with the recurrent CPr in patients with comorbid pathology, OS was more pronounced, which was manifested in a significantly greater increase in LPO and a decrease in AOD factors. Perhaps increased free radical activity is one of the factors involved in the pathogenesis of the inflammatory syndrome in patients with CP and comorbid pathology.

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Source of support: Nil; Conflicts of interest: None Declared