

# The Impact of Urolithiasis in the Adaptive Response of the Organism

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## Abstract

**Aim:** The aim of this study was to identify the impact of urolithiasis in the adaptive response of the organism.

**Methods:** We studied 108 patients with urolithiasis including men ( $N_1 = 51$ ) with a mean age of  $64.5 \pm 1.4$  years and women ( $N_2 = 57$ ), with an average age of  $68.2 \pm 1.7$  years ( $P > 0.05$ ). Three groups of methods applied. (1) Immunological and immunoassay studies (determination of cellular, humoral immunity, and phagocytic activity of peripheral blood leukocytes). Population structure of lymphoid cells was studied by immunofluorescence microscopy using monoclonal antibodies ("MedBioSpektr," Moscow). To assess the functioning of the hypothalamic-pituitary-adrenal cortex performed quantification of cortisol in the blood serum by solid-phase enzyme immunoassay. The reagent kit "A-8758 Alpha Interferon - EIA-BEST" and "A-8752 Gamma Interferon - EIA-BEST" (JSC "VECTOR-BEST," Novosibirsk) were used for quantification of interferon - alpha and IFN - gamma. (2) Methods of studying the structure of the urinary system. Radiation research for topical verification stones and renal status and upper urinary tract was performed according to the standard medical care for patients with urolithiasis (order of the Ministry of Health and Social Development of the Russian Federation, November 30, 2005, No. 704). Radionuclide indication of inflammatory lesions in the kidney scintigraphic studies performed in a planar mode gamma camera "CF-9200" ("Gamma," Hungary). (3) Methods of functional studies: To determine the adaptive capacity was used to create a computer program and the data on myocardial hemodynamic homeostasis received through tetrapolar chest rheography. **Results and Discussion:** The study showed that 48.7% of patients with urolithiasis had a satisfactory adaptation, 24.4% were in a state of tension of adaptive mechanisms, and 26.9% were identified a poor adaptation and failure of adaptation processes. **Conclusion:** It is established that the manifestation of the clinical picture of the disease provokes the formation of disintegrating types of hemodynamics and a decrease in the adaptive capacity of the organism. The course of the inflammatory process and a produced phlogogenic potential of leukocytes contributes to the development of the stress response with immune-neuroendocrine interactions.

**Key words:** Adaptive reactions of the body, chronic systemic inflammation, glucocorticoid changes, regulation of autonomic functions, systemic hemodynamics, the blood system status, urinary system

## INTRODUCTION

In recent studies,<sup>[1]</sup> a degradation of membrane structures that is detected in urolithiasis provokes the infiltration by polymorphonuclear leukocytes and lymphocytes of the interstitial space of the kidney. This space is actively communicates with vascular and tubular apparatus. This leads to the aseptic and bacterial inflammatory lesion<sup>[2]</sup> and often in subclinical manifestations.<sup>[3]</sup>

In the cellular ensemble of inflammation in the first line are cells of phagocytosis. One of the main indicators in the functional assessment of phagocytes is their ability to migrate to the area

of inflammation.<sup>[4]</sup> An active migration of phagocytes in the renal parenchyma at the disorders of urine outflow through the ureter can be proved by the data of scintigraphy with labeled leukocytes. Migration of leukocytes into the renal parenchyma occurs even at the preserved flow of urine in the upper urinary tract.

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It is important to emphasize that the cases were analyzed in the absence of clinically and laboratory confirmed pyelonephritis.

Pro-inflammatory cytokines are potent stimulators of phlogogenic that triggers the development of systemic stress reactions in response to stimuli of non-antigen nature. Accumulation of pro-inflammatory cytokines in the blood and the implementation of their regulatory effects are currently seen from a perspective of a systemic inflammatory response syndrome (SIRS).<sup>[5]</sup> While stress-related hormones (glucocorticoids and catecholamines) play the role of the factors of a feedback, aimed at the inhibition of secretion of cytokines and limiting the expansion of the inflammatory process. Emphasizing the relevance of the study, it is worth mentioning that Baevsky (1979) noted that the disease, despite of the specific anatomic-morphological localization, always is a disease of the whole organism, rather than a separate organ.<sup>[3]</sup> The nature of the response of the body as a deterministic system depends on the state of all its systems. Later, Petlenko *et al.* (1978) emphasized that the disease is always a unity of the general and local.<sup>[6]</sup>

## MATERIALS AND RESEARCH METHODS

### General characteristics of patients

Were studied 108 patients with urolithiasis including men ( $N_1 = 51$ ) with a mean age of  $64.5 \pm 1.4$  years and women ( $N_2 = 57$ ), with an average age of  $68.2 \pm 1.7$  years ( $P > 0.05$ ).

Inclusion criteria were as follows: Verification of diagnosis of urolithiasis with a parallel use of clinical and instrumental diagnostic tests package (sections N 20.0, N 20.1, N 22\*, Q 63.1 in ICD-10), with the history of the urolithiasis from 1 year or renal colic, with the absence of gynecological disease in women, and with no severe infravesical obstruction benign hyperplasia of the prostate in men.

The exclusion criteria were as follows: Organic mental disorders, mental disorder caused by the consumption of drugs, schizophrenia, developmental disorders (psychological), mental retardation, senile dementia, and neurotic disorders in the present or in the past time. Among the registered somatic diseases in men ( $n = 51$ ) and women ( $n = 57$ ) in the first place are hypertension (34 and 46, respectively), coronary heart disease (32 and 19), diseases of the gastrointestinal tract (13 and 29), and diseases of the biliary tract (9 and 36). It is seen that cardiovascular diseases are prevalent and manifest multiple two or three systemic pathologies, more common in women.

Hematuria was in 9.2% of patients. The average disease history was of  $6.6 \pm 1.5$  years. The recurrent urolithiasis was diagnosed in 23.2% of patients.

## RESEARCH METHODS

### Immunological and immunoassay research methods

As the material for the study of the parts of the immune system was heparinized, venous blood obtained from the cubital vein.

The examination included a determination of parameters of cellular, humoral immunity, and phagocytic activity of peripheral blood leukocytes. A population composition of lymphoid cells was studied by immunofluorescence microscopy with the use of monoclonal antibodies ("MedBioSpektr," Moscow).

To assess the functioning of the hypothalamic-pituitary-adrenal cortex was carried out the quantitative determination of cortisol level in serum by the method of solid-phase enzyme immunoassay.

For the quantitative determination of interferon- $\alpha$  and interferon- $\gamma$  was applied to a set of reagents "A-8758 Alpha-Interferon - IFA-BEST" and "A-8752 Gamma-Interferon - IFA-BEST" (CJSC "VECTOR-BEST," Novosibirsk).

### Methods of studying the structure of the urinary system

Radiation studies for topical verification of concrements and a condition of kidney and upper urinary tract were performed according to a standard medical care for patients with urolithiasis (order of the Ministry of Health and Social Development of the Russian Federation, November 30, 2005, No. 704).

Radionuclide indication of inflammatory lesions in renal was carried out by the scintigraphic study in planar mode on gamma camera MB 9200 (firm "Gamma," Hungary).

### Methods for functional studies

For definition of adaptive capacity was used a created computer program, and a data of myocardial-hemodynamic homeostasis obtained by tetrapolar chest rheography. In the development of computer programs (certificate of the official registration of computer programs No. 2006613561) was taken into the consideration the integrated physiological mechanisms and their individual-typological differences in the individual components.<sup>[7]</sup> Using the compiled computer program was identified an integral phagocytic index (interferon inducible genes [IFI]). The obtained results were analyzed with taking into an account the grades: IFI = 0.0-2.1 - satisfactory adaptation (there is a sufficient functional possibility [FP] of an organism, and homeostasis is maintained with the minimum

stress of regulatory systems); IFI = 2.2-3.3 - stress of adaptation mechanisms (FP is not reduced, and homeostasis is maintained by stress of regulatory systems); IFI = 3.3-4.3 - unsatisfactory adaptation (FP is reduced, and homeostasis is maintained at a significant stress of regulatory systems); and IFI  $\geq$ 4.3 - breakdown of adaptation (a sharp decline in FP, homeostasis is violated).<sup>[8]</sup>

The calculation of vegetative index of Kerdo.

## RESULTS AND DISCUSSION

The development of inflammatory changes in the body depends not only because of the local events.<sup>[9-17]</sup> The identified hyperinterferonemia in this study can be recognized as the systemic and attributive sign of SIRS in urolithiasis. The circulating in the blood interferons activates the hypothalamic-pituitary-adrenal system and provokes the development of the stress response. In turn, a decrease of the sensitivity to stress hormones that accompany the stress reaction exacerbates the pro-inflammatory changes in the kidneys.

### The condition of the blood system

In the study of hemogram indicators were marked changes, reflecting the processes of compensatory mobilization of the whole system. Clinical manifestation of urolithiasis was accompanied by a stereotyped reaction of the main types of leukocytes on the phlogogenic effects in the increase of their content and increase in the proportion of neutrophil population. There was a statistically significant increase of index of Kalf-Kalif: At clinical confirmation of infectious complications -  $3.7 \pm 0.2$ , in the absence of them -  $3.2 \pm 0.2$  (control -  $1.7 \pm 0.1$ ), and the reduction of lymphocytic index (respectively):  $0.25 \pm 0.02$  and  $0.37 \pm 0.02$ . The detected changes of the hemogram indicators are consistent with the literature data, reflecting the reaction of the blood system for inflammatory processes.<sup>[18,19]</sup> Malyshev *et al.* (1997), in the experiment, were revealed in aseptic inflammatory process the eosinopenic effect, typical for the alarm stage of the stress response, which is replaced by eosinophilia after 24-27 h, which determines the transition of alarm stage into the stage of a resistance.<sup>[7]</sup> In our studies, during the clinical debut of the urolithiasis was observed eosinophilia: In the presence of inflammatory complications -  $3.2 \pm 0.4\%$ , in their absence -  $3.7 \pm 0.3\%$ , which is typical in the resistance stage of stress reaction.

The results of examining of the reactivity of the immune system have shown that the dynamics of changes had affected all parts of the immune system and had a multidirectional nature. Urodynamic disorders did not affect the nature of the immune shifts ( $P > 0.05$ ). Was marked a relative decrease in the intensity of phagocytosis: Nitro blue tetrazolium (NBT) test is spontaneous at (hereinafter respectively): The absence of clinical evidence of inflammatory complications -  $16.4 \pm 1.9\%$ ,

in the presence of inflammatory complications -  $16.9 \pm 1.7\%$ ; NBT test induced:  $36.0 \pm 1.8\%$  and  $36.6 \pm 1.7\%$ , respectively. Was recorded a statistically significant decrease in the number of lymphocytes:  $26.8 \pm 1.4\%$  and  $28.2 \pm 1.4\%$ ; in the number of cells:  $7.0 \pm 0.6\%$  and  $9.1 \pm 0.9\%$ ; and in the increase of circulating immune complexes:  $55.2 \pm 5.3$  c.u. and  $74.6 \pm 5.1$  c.u.

For the detection of specific features of the immune system values in the studied groups was performed a discriminant analysis. The data, measured in the absolute units, were transformed by Freeman-Tukey  $y' = \sqrt{y} + \sqrt{y+1}$ , and the relative indicators - into the angle  $\varphi$ -transformation,  $y' = 2 \arcsin \sqrt{p}$ , where  $p$  is the rate indicator in the unit shares and the arcsine is expressed in radians.

The results of the discriminant analysis of immunological parameters are presented in Table 1.

As can be seen from Table 1, during the analysis was isolated a discriminant function having a high statistical significance (Wilks  $\lambda = 0.385$ ,  $\chi^2_{[19]} = 129.25$ ,  $P < 0.00001$ ) - an increasing of leukocytes levels and circulating immune complexes, the decreasing of lymphocytes number, mostly B-lymphocytes.

To reflect the patterns of change in components of the immune system, the obtained results were subjected to processing by the method of principal components followed by a rotation of factor structures on the principle of varimax. The results of the statistical processing are presented in Table 2.

As shown in Table 2, the largest informative load carries the 1<sup>st</sup> factor which is directly proportional to the number and percentage of lymphocytes, leukocyte count, CD<sub>3</sub>, and CD<sub>22</sub>. Next in importance is the 2<sup>nd</sup> factor, it combines with a positive connection CD<sub>8</sub> and with a negative connection the immunoregulatory index.

As the result of this study, it was shown, on the one hand, the decrease in the number of total and mature B-lymphocytes, and on the other hand, it was observed an excessive response, characterized by increased levels of circulating immune complexes.

The weakening of the cooperation processes between components of the immune system creates the possibility of a development of the inflammatory process.<sup>[6]</sup> The study of indicators of NBT test showed the inhibition of the oxygen-dependent anti-infective activity of enzyme systems of phagocytes and a decrease in their functional capacity. A similar situation is described in inflammatory processes, when despite the intensification of oxygen metabolism of phagocytes, there is a decrease in their microbial functions.<sup>[20]</sup> The mentioned inferiority of phagocytic reactions leads to a long-term preservation of the inflammatory process in renal tissue. Lebedev *et al.* (2005) noted a permanent increase in the level of interconnectedness of the individual links

**Table 1:** The results of the discriminant analysis of immunological parameters

Indicator and units of measure	Standardized canonical function coefficient	The correlation of the indicator with the canonical variable
1	2	3
Leukocytes (abs)	0.775	0.308
Phagocytic index of neutrophils (%)	-0.357	-0.254
Spontaneous NBT test of neutrophils (%)	0.019	0.020
Spontaneous NBT test of induced neutrophils (%)	0.107	-0.029
Lymphocytes (%)	0.205	-0.309
Lymphocytes (abs)	-0.711	-0.053
CD <sub>3</sub> (%)	-0.571	0.072
CD <sub>4</sub> (%)	0.211	0.110
CD <sub>8</sub> (%)	0.490	0.163
CD <sub>22</sub> (%)	-0.353	-0.361
IgA (g/L)	-0.037	0.036
IgG (g/L)	0.019	0.044
IgM (g/L)	-0.223	-0.028
Circulating immune complexes (c.u.)	0.723	0.587
Circulating immune complexes (the small size)	-0.132	-0.009
Complement, CH <sub>50</sub>	0.057	0.160

Highlighted - ratios >3. NBT: Nitro blue tetrazolium

**Table 2:** The results of a factor analysis of components of the immune system in patients with urolithiasis

The proportion of factors	Significant	R
1 <sup>st</sup> factor: Dispersion - 13.6%	Lymphocytes (number)	0.966
	CD <sub>3</sub> (number)	0.923
	Lymphocytes (number)	0.591
	CD <sub>22</sub> (number)	0.454
	Lymphocytes (%)	0.453
2 <sup>nd</sup> factor: Dispersion - 9.5%	CD <sub>8</sub> (%)	0.813
	Immunoregulatory index	-0.980

in conditions of chronic inflammation.<sup>[21]</sup> In our studies, we found a strong negative correlation in immunological pair of neutrophils-lymphocytes (-0.89 in the absence of inflammatory manifestations in the kidney and -0.88 in the presence) ( $P < 0.001$ ) and a weak positive correlation in a pair IgM-IgG (+0.04 and -0.22) ( $P < 0.001$ ), indicating the transition to a lower level of health.

### Features of systemic hemodynamics and regulation of autonomic functions

In the study of systemic hemodynamics, it was observed a hemodynamic heterogeneity in the observed groups.

Large spread of values of cardiac and stroke indexes and a total peripheral vascular resistance in the groups that were selected by gender allowed each of them to divide the indicators into three types. Hyperkinetic type was identified in 18.5% of men and 55.3% of women; eukinetic - in 20.1% and 17.3%, hypokinetic - in 61.4% and 27.4%. An average hemodynamic pressure was recorded in men -  $101.1 \pm 1.3$  mm Hg, and in women, it was  $96.9 \pm 1.5$  mm Hg ( $P < 0.001$ ). The higher numbers of an average hemodynamic pressure, reflecting the degree of tonic tension of the arteriolar system, were recorded in men compared to women.

In hyperkinetic type, the key mechanism for maintaining an optimal average hemodynamic pressure was the cardiac index (here and hereafter), in men -  $4.4 \pm 0.2$  and in women -  $2.8 \pm 0.1$  L/min/m<sup>2</sup>, on the background of significantly higher values of a stroke index -  $65.3 \pm 2.9$  and  $39.9 \pm 1.3$  ml/m<sup>2</sup>, while the total peripheral vascular resistance was the lowest -  $1013.4 \pm 61.8$  and  $1701.8 \pm 59.4$  dean·s/cm<sup>5</sup>/m<sup>2</sup>.

In eukinetic type, the cardiac index decreased -  $3.1 \pm 0.1$  and  $1.8 \pm 0.1$ , on the background of a decreased stroke index -  $45.3 \pm 1.6$  and  $25.8 \pm 1.3$ , and a total peripheral vascular resistance, on the contrary, increased -  $1349.5 \pm 50.2$  and  $2405.2 \pm 118.8$ .

In hypokinetic type, the total peripheral vascular resistance was the highest ( $2207.6 \pm 76.8$  and  $3938.4 \pm 351.9$ ) as the cardiac index ( $2.0 \pm 0.1$  and  $1.3 \pm 0.1$ ) and stroke index ( $31.3 \pm 0.9$  and  $19.8 \pm 1.8$ ) were the smallest.

The typological data had statistically significant differences ( $P < 0.001$ ), with  $r$  on the average hemodynamic blood pressure from  $-0.65$  to  $-0.97$ , cardiac index from  $-0.44$  to  $-0.61$ , stroke index from  $-0.68$  to  $0.44$ , and the total peripheral vascular resistance from  $-0.36$  to  $0.36$ . The differences were statistically significant in the cases of the presence and absence of pyelonephritis. Analysis of the indicators allows us to conclude that patients with urolithiasis have a reduced adaptive capacity with the increase in hypokinetic type in energy - consuming indicators of an average hemodynamic blood pressure and a total peripheral vascular resistance.

Literature data indicate that at the hyperkinetic type of hemodynamics, the sympathotonic reactions make a regulatory priority, in hypokinetic type - a vagotonic.<sup>[22-24]</sup>

The greatest number of correlation relationship is observed between the disintegration of the autonomic regulations, as a consequence, the change in hemodynamic parameters and functional indicators of kidneys of patients with hyperkinetic and hypokinetic types of blood circulation. That determines the tension of regulatory mechanisms in these polar types and allocates them as with a poor prognosis. In our studies, it was found that up to 84% of men and 87% of women had specified disintegrative types of hemodynamics.

## CONCLUSION

The study of the nature of vegetative reactions by index of Kerdo has shown the prevalence of negative values in patients with urolithiasis, compared with the control group ( $\chi^2 > 3.841$ ,  $P < 0.001$ ). It was an evidence of the excitation of the parasympathetic division of the autonomic nervous system, leading to the increased activity of bioenergetic systems, the rise of hypokinetic type, vasodilation of renal blood vessels, and increase of a motor activity of the urinary tract.

A study of the adaptation possibilities of organism on the basis of vegetative homeostasis showed that 48.7% of patients with urolithiasis had a satisfactory adaptation, 24.4 % in a state of a tension of adaptive mechanisms, and 26.9% in a state of identified poor adaptation and failure of adaptation processes.

A study of hematological parameters and immune system testified to the fact that the main reactive processes with the increasing of a number of cell composition, but with the oppression of their functional activity, occur in the phagocytic link and in the system of nonspecific resistance. In cellular and humoral immunity, the reactivity was reduced. An imbalance in the immune homeostasis and the imperfections of the current reactions provide the possibility of chronic inflammatory process in the kidney and the prospect of the beginning of autoimmune mechanisms.

Thus, the presented data suggest that the presence of urolithiasis in the majority of cases determines the voltage adaptive reactions of the body and poor adaptation.

Patients of elderly and senile age with urolithiasis are at the risk of hyperinterferonemia. They should be recommended of studying of blood interferons and a therapy of a chronic systemic inflammation by glucocorticoids and nonsteroidal anti-inflammatory drugs in conventional schemes even in the absence of clinical manifestations of pyelonephritis.

A further comprehensive study of the characteristics of the inflammatory process and a produced phlogogenic potential of leukocytes may contribute to the correction of the development of the stress response with immune-neuroendocrine interactions.

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