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# URIC ACID, NEUROENDOCRINE-IMMUNE COMPLEX AND METABOLISM: RELATIONSHIPS

**Igor L. Popovych[1,2], https://orcid.org/0000-0002-5664-5591**
**Igor S. Bombushkar[2], https://orcid.org/0000-0003-4260-0736**
**Xawery Żukow[3], https://orcid.org/0000-0001-5028-7829**
**Halyna Y. Kovalchuk[4], https://orcid.org/0000-0002-5261-8422**

**[1]OO Bohomolets Institute of Physiology of NAS of Ukraine, Kyïv, Ukraine**
**i.popovych@biph.kiev.ua**
**[2]Ukrainian Scientific Research Institute of Medicine of Transport, Odesa, Ukraine**
**bombuchkar@gmail.com**
**[3]Medical University of Bialystok, Bialystok, Poland**
**xaweryzukow@gmail.com**
**[4]Ivan Franko State Pedagogical University, Drohobych, Ukraine**
**galynakovalchuk5@gmail.com**

## Abstract

**Background**. During the implementation of the project "Physiological activity of uric acid", our group discovered four variants of the combination of levels of uricemia and uricosuria in patients with chronic pyelonephritis in the remission phase, which are accompanied by characteristic constellations of parameters of the central and autonomic nervous, endocrine, and immune systems, as well as the exchange of nitrogenous metabolites and electrolytes, the levels of which correlate with uricemia and/or uricosuria. The **aim** of this study is to clarify the relationship between parameters of uric acid exchange and neuroendocrine-immune complex as well as other metabolites. **Materials and methods.** Under an observations were 34 males (23-70 years) and 10 females (33-76 years) with chronic pyelonephritis in the phase of remission. The main object of the study was serum and urine levels of uric acid. Other metabolic, endocrine and immune parameters were determined in the same blood and urine samples. In addition, EEG and HRV was recorded almost synchronously. **Results**. Among all registered parameters, 28 were identified as characteristic of the four variants of uric acid metabolism. The discriminant model includes, in addition to uricosuria and uricemia by definition, 10 neuroendocrine, 5 immune, and 6 metabolic parameters, as well as bacteriuria, *Bifidobacteria* of feces, entropy of immunocytogram and Popovych's leukocytogram strain index. According to the results of the canonical correlation analysis, it was established that balneotherapy-induced concomitant changes in uricosuria and uricemia positively determine changes in, first, the PSD of the theta-rhythm in the T3 locus and beta-rhythm in the O2 locus

aa well as HRV-markers of vagal tone and sympatho-vagal balance; secondly – diuresis and excretion of urea, magnesium, sodium, phosphates, calcium, potassium and chloride, as well as calciumemia and magnesiumemia; thirdly – serum IgG and CIC. Instead, changes in cortisolemia and testosteroneemia as well as TNF-alpha and the intensity of Staph. aureus phagocytosis are subject to negative determination. In general, the rate of uric acid determination of the dynamics of the listed parameters of the body is 96%. **Conclusion**. The uric acid molecule, as a structural analog of methylxanthines and adenosine, exerts effects on neurons, endocrinocytes, and immunocytes, presumably through their adenosine receptors, and the metabolic effects of uric acid are the consequences of its neuro-endocrine effects.
***Keywords***: uric acid, EEG, HRV, adaptation hormones, immunity, electrolytes, urea, creatinine, relationships.

## INTRODUCTION

During the implementation of the project "Physiological activity of uric acid" [13,44], our group discovered four variants of the combination of levels of uricemia and uricosuria in patients with chronic pyelonephritis in the remission phase, which are accompanied by characteristic constellations of parameters of the central [7] and autonomic [5] nervous, endocrine [5], and immune [18,19,54] systems, as well as the exchange of nitrogenous metabolites and electrolytes [13], the levels of which correlate with uricemia and/or uricosuria. Similar tests, with the exception of EEG, were conducted in an experiment on healthy rats [3,4,14-17,43]. The **aim** of this study is to clarify the relationship between parameters of uric acid exchange and neuroendocrine-immune complex as well as other metabolites, that will allow to create a complete picture of the physiological activity of uric acid.

## MATERIALS AND METHODS

Under an observations were 34 males (23-70 years) and 10 females (33-76 years) with chronic pyelonephritis in the phase of remission. Testing was performed twice - on admission and after 7-10 days of standard balneotherapy on Truskavets Spa (drinking of Naftussya bioactive water, applications of ozokerite, mineral pools) [45].

The main object of the study was serum and urine levels of uric acid (estimated by uricase method [11]).

EEG recorded a hardware-software complex “NeuroCom Standard” (KhAI Medica, Kharkiv, Ukraine) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10-20 international system, with the reference electrodes A and Ref on the earlobes. Two minutes after the eyes had been closed, 25 sec of artifact free EEG data were collected by computer. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), absolute ($\mu V^2$/Hz) and relative (%) power spectral density (PSD) of basic rhythms: β (35÷13 Hz), α (13÷8 Hz), θ (8÷4 Hz) and δ (4÷0,5 Hz) in all loci, according to the instructions of the device.

In addition, calculated coefficient of Asymmetry (As) and Laterality Index (LI) for PSD each Rhythm using equations [39]:

As, % = 100•(Max – Min)/Min; LI, % = Σ [200•(Right – Left)/(Right + Left)]/8.

We draw attention to the existence of an alternative equation for calculating Laterality [57]:

(Left − Right)/(Left + Right).

We calculated also for each locus EEG the Entropy (h) of normalized PSD using Popovych’s IL [12,13,42,45,51] equation based on classic Shannon’s CE [53] equation:

$hEEG = - [PSD\alpha \bullet \log_2 PSD\alpha + PSD\beta \bullet \log_2 PSD\beta + PSD\theta \bullet \log_2 PSD\theta + PSD\delta \bullet \log_2 PSD\delta]/\log_2 4$.

Simultaneosly recorded electrocardiogram in II lead to assess the parameters of HRV (software and hardware complex "CardioLab+HRV" produced by "KhAI-MEDICA", Kharkiv, Ukraine). For further analysis the following parameters heart rate variability (HRV) were selected. Temporal parameters (Time Domain Methods): heart rate (HR), mode (Mo), the standart deviation of all NN intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the percent of interval differences of successive NN intervals greater than 50 msec ($pNN_{50}$); triangular index (TNN). Spectral parameters (Frequency Domain Methods): power spectral density (PSD) bands of HRV - high-frequency (HF, range 0,4÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,04÷0,015 Hz) and ultralow-frequency (ULF, range 0,015÷0,003 Hz) [2,52]. We calculated the Entropy of HRV band [42] and classical indexes LF/HF and LFnu=100%•LF/(LF+HF) as well as (VLF+LF)/HF as Centralization Index. Baevskiy's RM parameters: the amplitude of mode (AMo) and variational scope (MxDMn) as well as author's indexes: Baevskiy's Stress Index (BSI=AMo/2•Mo•MxDMn) and Baevskiy's Activity Regulatory Systems Index (BARSI) [2].

Among hormones determined main adaptation hormones such as Cortisol, Aldosterone, Testosterone, Triiodothyronine as well as Calcitonin (by the ELISA with the use of analyzers "Tecan" and "RT-2100C" and corresponding sets of reagents from "Алкор Био", XEMA Co, Ltd and DRG International Inc).

Immune status evaluated as described in the manual [34]. For phenotyping subpopulations of lymphocytes used the methods of rosette formation with sheep erythrocytes on which adsorbed monoclonal antibodies against receptors CD3, CD4, CD8, CD25, CD22 and CD56 from company "Granum" (Kharkiv) with visualization under light microscope with immersion system. Subpopulation of T cells with receptors high affinity determined by test of "active" rosette formation. The state of humoral immunity judged by the concentration in serum of Immunoglobulins of classes G, A, M (ELISA, analyser "Immunochem", USA) and circulating immune complexes (by polyethylene glycol precipitation method) as well as C-reactive protein (by the ELISA with the use of analyzer "RT-2100C"), Tumor Necrosis Factor-α, Interleukins 1β and 6 (ELISA, analyzer "Stat Fax 303", USA, reagents from "Vector-Best", RF).

In portion of the capillary blood we counted up Leukocytogram and calculated the Entropy (h) of Leukocytogram (LCG) as well as its Strain Index using Popovych's IL [45,46] equations:

$$hLCG = - [L \bullet \log_2 L + M \bullet \log_2 M + E \bullet \log_2 E + PMNN \bullet \log_2 PMNN + RSN \bullet \log_2 RSN]/\log_2 5;$$

$$\text{Strain Index-1} = [(Eos/3{,}5\text{-}1)^2 + (RSN/3{,}5\text{-}1)^2 + (Mon/5{,}5\text{-}1)^2 + (Leuk/6\text{-}1)^2]/4;$$

$$\text{Strain Index-2} = [(Eos/2{,}75\text{-}1)^2 + (RSN/4{,}25\text{-}1)^2 + (Mon/6\text{-}1)^2 + (Leuk/5\text{-}1)^2]/4.$$

Parameters of phagocytic function of neutrophils estimated as described by Kovbasnyuk MM [27,48]. The objects of phagocytosis served daily cultures of Staphylococcus aureus (ATCC N 25423 F49) as typical specimen for Gram-positive Bacteria and Escherichia coli (O55 K59) as typical representative of Gram-negative Bacteria. Take into account the following parameters of Phagocytosis: activity (percentage of neutrophils, in which found microbes - Hamburger's Phagocytic Index PhI), intensity (number of microbes absorbed one phagocytes - Microbial Count MC or Right's Index) and completeness (percentage of dead microbes - Killing Index KI).

The condition of microbiota is evaluated on the results of sowing of feces. The levels of bacteriuria, leukocyturia, and erythrocyturia were also assessed by routine methods.

Daily urine was collected, in which was determined the concentration of electrolytes: calcium (by reaction with arsenase III), magnesium (by reaction with colgamite), phosphates (phosphate-molybdate method), chloride (mercury-rhodanidine method), sodium and potassium (flamming photometry); nitric metabolites: creatinine (by Jaffe's color reaction by

Popper's method) and urea (urease method by reaction with phenolhypochlorite). The same metabolic parameters were determined in plasma as well as glucose (glucose-oxidase method). The analysis carried out according to instructions [11] with the use of analyzers "Reflotron" (BRD) and "Pointe-180" (USA) and corresponding sets of reagents.

Given its integral physiological nature [20,30-33], we determined also the electrokinetics index (EKI) as rate of electronegative nuclei of buccal epithelium by intracellular microelectrophoresis on the device "Biotest" (Kharkiv State University).

Normal (reference) values of variables are taken from the instructions and/or database of the Truskavetsian Scientific School of Balneology [12,13,45].

For statistical analysis used the software package "Statistica 6.4".

**RESULTS**

Discriminant analysis was used to identify the specific accompaniment of clusters of uric acid exchange [25]. From among all the registered parameters, the forward stepwise program selected 28 as identifiers for the four variants of uric acid metabolism. The discriminant model includes (Tables 1 and 2), in addition to uricosuria and uricemia by definition, 10 **neuroendocrine** parameters (6 EEG, vagal tone, indices of sympatho-vagal balance of Kerdö and Baevsky, calcitonin), 5 parameters of **immunity** (activity and completion of phagocytosis by neutrophils of gram-positive bacteria, the level of total lymphocytes and IgG in the blood and IgA in saliva), two **informational** parameters (Popovych's strain index of the leukocytogram and the entropy of the immunocytogram), 6 parameters of **metabolism** (serum magnesium, potassium, phosphates and creatinine, creatinineuria, body mass index), as well as markers of chronic pyelonephritis (**bacteriuria**) and microbiota (***Bifidobacteria***).

**Table 1. Summary of step-by-step analysis of parameters of uric acid exchange, metabolism and neuroendocrine-immune complex, ranked by Λ**

| **Variables currently in the model** | F to enter | p-level | **Λ** | F-value | p-level |
|---|---|---|---|---|---|
| **Uricosuria, mM/24 h** | 154 | 0 | 0,154 | 154 | $10^{-6}$ |
| **Uricemia normalized, Z** | 13,5 | $10^{-6}$ | 0,104 | 58,3 | $10^{-6}$ |
| **PSD T4-δ, μV²/Hz** | 3,96 | 0,011 | 0,090 | 37,4 | $10^{-6}$ |
| **PSD O2-θ, %** | 3,51 | 0,019 | 0,080 | 28,6 | $10^{-6}$ |
| **Laterality δ, %** | 3,40 | 0,022 | 0,071 | 23,7 | $10^{-6}$ |
| **Calcitonin, ng/L** | 3,01 | 0,035 | 0,064 | 20,5 | $10^{-6}$ |
| **Phagocytose Index vs Staphylococcus aureus, %** | 2,37 | 0,077 | 0,058 | 18,1 | $10^{-6}$ |
| **Bacteriuria, points** | 3,11 | 0,031 | 0,052 | 16,5 | $10^{-6}$ |
| **PSD C4 Entropy** | 2,25 | 0,090 | 0,048 | 15,1 | $10^{-6}$ |
| **PSD F4 Entropy** | 2,70 | 0,052 | 0,043 | 14,1 | $10^{-6}$ |
| **Pan-Lymphocytes of Blood, %** | 2,36 | 0,078 | 0,039 | 13,2 | $10^{-6}$ |
| **Kerdö Vegetative Index, units** | 3,08 | 0,033 | 0,035 | 12,7 | $10^{-6}$ |
| **Bactericidity vs Staphyl. aureus, $10^9$ Bacteria/L** | 3,97 | 0,011 | 0,030 | 12,4 | $10^{-6}$ |
| **IgA Saliva, mg/L** | 3,54 | 0,019 | 0,026 | 12,2 | $10^{-6}$ |
| **IgG Serum, g/L** | 2,06 | 0,114 | 0,024 | 11,6 | $10^{-6}$ |
| **PSD C3-δ, %** | 1,68 | 0,180 | 0,022 | 11,1 | $10^{-6}$ |
| **Popovych's Strain Index-1, points** | 2,12 | 0,106 | 0,020 | 10,7 | $10^{-6}$ |
| **AMo/MxDMn as Sympatho-vagal balance Index** | 1,90 | 0,138 | 0,019 | 10,4 | $10^{-6}$ |
| **Body Mass Index, kg/m²** | 2,21 | 0,096 | 0,017 | 10,1 | $10^{-6}$ |
| **Magnesium Plasma, mM/L** | 1,84 | 0,149 | 0,016 | 9,80 | $10^{-6}$ |
| **Phosphates Plasma, mM/L** | 1,46 | 0,235 | 0,015 | 9,46 | $10^{-6}$ |
| **Potassium Plasma, mM/L** | 1,77 | 0,162 | 0,014 | 9,20 | $10^{-6}$ |
| **Uricemia, mM/L** | 1,69 | 0,179 | 0,013 | 8,96 | $10^{-6}$ |
| **RMSSD, msec** | 1,69 | 0,179 | 0,012 | 8,75 | $10^{-6}$ |
| ***Bifidobacteria* faeces, lg CFU/g** | 2,85 | 0,045 | 0,010 | 8,75 | $10^{-6}$ |
| **Entropy of Immunocytogram** | 1,22 | 0,312 | 0,010 | 8,48 | $10^{-6}$ |
| **Creatinine Plasma, μM/L** | 1,21 | 0,313 | 0,009 | 8,24 | $10^{-6}$ |
| **Creatininuria, mM/24 h** | 1,18 | 0,327 | 0,008 | 8,00 | $10^{-6}$ |

**Table 2. Summary of discriminant function analysis for parameters of uric acid exchange, metabolism and neuroendocrine-immune complex**

Step 28, N of vars in model: 28; Grouping: 4 grps; Wilks' Λ: 0,0085; approx. $F_{(84)}$=8,0; $p<10^{-6}$

| Variables currently in the model | Clusters of Uric Acid Exchange (Males/Females) | | | | Parameters of Wilks' Statistics | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | S- E2+ IV (18/4) | S± E+ I (16/5) | S2- E+ II (14/1) | S± E- III (20/10) | Wilks Λ | Par-tial Λ | F-re-mo-ve | p-level | Tole-ran-cy | Refe-rence Cv/**σ** |
| **Uricosuria, mM/24 h** | 5,94 | 3,94 | 3,88 | 2,27 | 0,076 | 0,112 | 150 | $10^{-6}$ | 0,396 | 3,00 0,250 |
| **Uricemia, mM/L** | 0,316 | 0,371 | 0,249 | 0,322 | 0,010 | 0,864 | 2,99 | 0,038 | 0,109 | 0,365 0,116 |
| **Uricemia normalized, Z-score** | -0,70 | +0,09 | -1,89 | -0,53 | 0,009 | 0,897 | 2,17 | 0,101 | 0,155 | 0 **0,5** |
| **PSD T4-δ, $\mu V^2$/Hz** | 57 | 354 | 94 | 161 | 0,009 | 0,984 | 0,31 | 0,818 | 0,543 | 92 1,091 |
| **PSD O2-θ, %** | 6,3 | 5,1 | 5,3 | 9,1 | 0,010 | 0,864 | 3,00 | 0,038 | 0,538 | 7,1 0,554 |
| **Laterality δ, %** | -9,6 | -24,9 | -27,5 | +6,8 | 0,010 | 0,891 | 2,33 | 0,084 | 0,610 | +2,5 **39,8** |
| **Calcitonin, ng/L** | 6,45 | 7,21 | 8,76 | 7,50 | 0,010 | 0,878 | 2,65 | 0,058 | 0,639 | 12,03 |
| **Calcitonin Males, ng/L** | 6,65 | 7,76 | 8,64 | 8,80 | | | | | | 13,95 0,493 |
| **Calcitonin Females, ng/L** | 5,55 | 5,48 | 10,39 | 4,90 | | | | | | 5,05 0,490 |
| **Phagocytose Index vs Staph. aureus, %** | 98,54 | 99,00 | 99,00 | 98,96 | 0,010 | 0,852 | 3,31 | 0,026 | 0,431 | 98,3 0,018 |
| **Bacteriuria, points** | 0,28 | 0,22 | 0,43 | 0,27 | 0,010 | 0,810 | 4,45 | 0,007 | 0,290 | 0 **0,24** |
| **PSD C4 Entropy** | 0,83 | 0,87 | 0,80 | 0,85 | 0,014 | 0,623 | 11,5 | $10^{-5}$ | 0,222 | 0,867 0,109 |
| **PSD F4 Entropy** | 0,81 | 0,71 | 0,80 | 0,81 | 0,010 | 0,822 | 4,12 | 0,010 | 0,295 | 0,851 0,139 |
| **Pan-Lymphocytes of Blood, %** | 34,6 | 31,7 | 35,8 | 33,9 | 0,012 | 0,683 | 8,84 | $10^{-4}$ | 0,166 | 32,0 0,174 |
| **Kerdö Vegetative Index, units** | -24 | -13 | -27 | -20 | 0,013 | 0,640 | 10,7 | $10^{-5}$ | 0,484 | -20 **23,6** |
| **Bactericidity vs Staph. aureus, $10^9$ Bacteria/L** | 93,8 | 103,0 | 90,6 | 94,5 | 0,010 | 0,813 | 4,37 | 0,008 | 0,322 | 105,7 0,100 |
| **IgA Saliva, mg/L** | 118 | 135 | 142 | 144 | 0,010 | 0,882 | 2,53 | 0,066 | 0,239 | 163 0,241 |
| **IgG Serum, g/L** | 14,4 | 15,1 | 14,5 | 15,6 | 0,009 | 0,930 | 1,42 | 0,246 | 0,602 | 12,75 0,206 |
| **PSD C3-δ, %** | 25,7 | 42,1 | 32,4 | 30,5 | 0,010 | 0,850 | 3,35 | 0,025 | 0,407 | 28,0 0,602 |
| **Popovych's Strain Index-1, points** | 0,13 | 0,25 | 0,16 | 0,13 | 0,009 | 0,975 | 0,48 | 0,699 | 0,479 | 0,067 0,722 |
| **AMo/MxDMn as Symp/Vagal balance** | 218 | 394 | 234 | 236 | 0,009 | 0,943 | 1,15 | 0,338 | 0,374 | 251 0,303 |
| **Body Mass Index, $kg/m^2$** | 27,5 | 28,1 | 25,9 | 26,9 | 0,010 | 0,855 | 3,22 | 0,029 | 0,461 | 24,2 0,133 |
| **Magnesium Plasma, mM/L** | 0,826 | 0,856 | 0,831 | 0,822 | 0,010 | 0,889 | 2,37 | 0,080 | 0,512 | 0,90 0,056 |
| **Phosphates Plasma, mM/L** | 0,96 | 0,97 | 1,09 | 1,06 | 0,009 | 0,895 | 2,23 | 0,094 | 0,581 | 1,20 0,167 |
| **Potassium Plasma,** | 4,40 | 4,40 | 4,50 | 4,19 | 0,010 | 0,893 | 2,27 | 0,091 | 0,570 | 4,55 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **mM/L** | | | | | | | | | | 0,104 |
| **RMSSD HRV, msec** | 30,6 | 27,4 | 32,6 | 26,1 | 0,010 | 0,869 | 2,87 | 0,044 | 0,291 | 28,8 ,486 |
| ***Bifidobacteria* faeces, lg CFU/g** | 5,74 | 5,49 | 5,40 | 5,66 | 0,010 | 0,885 | 2,48 | 0,070 | 0,398 | 6,94 0,011 |
| **Entropy of Immunocytogram** | 0,967 | 0,967 | 0,964 | 0,956 | 0,009 | 0,910 | 1,88 | 0,143 | 0,486 | 0,960 0,059 |
| **Creatinine Plasma, µM/L** | 85,6 | 87,4 | 88,1 | 84,0 | 0,009 | 0,924 | 1,55 | 0,211 | 0,363 | 77,5 0,172 |
| **Creatininuria, mM/24 h** | 9,43 | 9,27 | 7,21 | 6,71 | 0,009 | 0,942 | 1,18 | 0,327 | 0,448 | 11,0 0,330 |

Note. For four variables, SD is given instead of Cv.

Instead, a number of parameters, despite their obvious recognition ability, were outside the discriminant model, apparently due to duplication/redundancy of information (Table 3).

**Table 3. Parameters of neuroendocrine-immune complex and metabolism, not included in the model**

| **Variables** | **Clusters of Uric Acid Exchange (Males/Females)** | | | | **Parameters of Wilks' Statistics** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **S- E2+ IV (18/4)** | **S± E+ I (16/5)** | **S2- E+ II (14/1)** | **S± E- III (20/10)** | Wilks Λ | Par-tial Λ | F to en-ter | p-level | Tole-ran-cy | Refe-rence Cv/**σ** |
| **PSD C3-δ, µV²/Hz** | 91 | 315 | 259 | 166 | 0,008 | 0,968 | 0,63 | 0,601 | 0,251 | 108 0,774 |
| **PSD T6-α, %** | 37,8 | 27,3 | 24,4 | 28,0 | 0,008 | 0,955 | 0,88 | 0,455 | 0,431 | 35,5 0,502 |
| **PSD F7-θ, µV²/Hz** | 15,8 | 42,7 | 29,1 | 28,3 | 0,008 | 0,979 | 0,40 | 0,752 | 0,302 | 18,2 0,843 |
| **PSD T4-δ, %** | 24,7 | 45,9 | 29,0 | 36,7 | 0,008 | 0,985 | 0,28 | 0,839 | 0,272 | 31,0 0,615 |
| **$(Ca/K)^{0.5}$ Plasma as Symp/Vagal balance** | 0,71 | 0,71 | 0,69 | 0,73 | 0,008 | 0,987 | 0,25 | 0,865 | 0,186 | 0,71 0,104 |
| **Triiodothyronine, nM/L** | 1,86 | 2,17 | 2,02 | 1,96 | 0,008 | 0,985 | 0,29 | 0,832 | 0,431 | 2,20 0,227 |
| **Cortisol, nM/L** | 531 | 475 | 432 | 563 | 0,008 | 0,952 | 0,94 | 0,430 | 0,750 | 405 0,524 |
| **Sex Index (M=2; F=1)** | 1,82 | 1,76 | 1,93 | 1,67 | 0,008 | 0,991 | 0,18 | 0,913 | 0,035 | 1,23 0,344 |
| **Testosterone normali-zed by sex&age, Z** | -0,12 | +0,55 | +1,03 | +0,22 | 0,008 | 0,985 | 0,28 | 0,837 | 0,581 | 0 **0,5** |
| Males, Z-score | -0,31 | +0,62 | +1,09 | +0,18 | | | | | | 0 |
| Females, Z-score | +0,70 | +0,22 | +0,12 | +0,29 | | | | | | 0 |
| **Calcitonin normalized by sex, Z** | -0,87 | -0,69 | -0,60 | -0,57 | 0,008 | 0,988 | 0,23 | 0,877 | 0,107 | 0 **0,5** |
| Males, Z-score | -1,07 | -0,90 | -0,78 | -0,75 | | | | | | 0 |
| Females, Z-score | +0,02 | -0,01 | +1,08 | -0,22 | | | | | | 0 |
| **Interleukin-1, ng/L** | 4,81 | 4,74 | 5,34 | 4,58 | 0,008 | 0,974 | 0,50 | 0,685 | 0,651 | 4,51 0,173 |
| **Killing Index vs Staph. aureus, %** | 49,5 | 53,0 | 47,9 | 47,9 | 0,008 | 0,991 | 0,16 | 0,922 | 0,350 | 58,9 0,142 |
| **$CD4^+CD3^+$ T-helper Lymphocytes, %** | 28,3 | 30,0 | 32,3 | 32,6 | 0,008 | 0,978 | 0,42 | 0,737 | 0,168 | 39,5 0,082 |
| **$CD8^+CD3^+$ T-cytolytic Lymphocytes, %** | 23,7 | 23,4 | 21,2 | 23,3 | 0,008 | 0,974 | 0,50 | 0,684 | 0,629 | 23,5 0,138 |
| **Leukocyturia, lg/mL** | 3,44 | 3,26 | 3,19 | 3,44 | 0,008 | 0,965 | 0,69 | 0,564 | 0,453 | 3,00 0,070 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Lactobacilli* faeces, lg CFU/g** | 6,48 | 6,31 | 6,14 | 6,38 | 0,008 | 0,963 | 0,72 | 0,543 | 0,016 | 8,10<br>0,015 |
| **Age, years** | 44,6 | 49,0 | 51,5 | 53,1 | 0,008 | 0,991 | 0,17 | 0,918 | 0,456 | 49,7<br>0,256 |
| **Electrokinetic Index, %** | 48,3 | 43,6 | 42,7 | 40,4 | 0,015 | 0,993 | 0,13 | 0,940 | 0,497 | 40,9<br>0,250 |
| **Glucose Plasma, mM/L** | 4,57 | 4,11 | 4,94 | 4,69 | 0,008 | 0,972 | 0,54 | 0,658 | 0,748 | 4,70<br>0,160 |

Next, we transform the 28-dimensional space of discriminant variables into the 3-dimensional space of canonical roots. The canonical correlation coefficient for the first root is 0,969 (Wilks' $\Lambda$=0,008; $\chi^2_{(84)}$=339; $p<10^{-6}$), for the second 0,837 (Wilks' $\Lambda$=0,140; $\chi^2_{(54)}$=139; $p<10^{-6}$), for the third 0,729 (Wilks' $\Lambda$=0,469; $\chi^2_{(26)}$=54; p=0,001). The major root contains 81,7% of the discriminant possibilities, the second – 12,3% and the minor - 6,0%.

Table 4 presents the standardized and raw coefficients for the discriminant variables needed to calculate the values of the discriminant roots for each person as the sum of the products of the raw coefficients by the individual values of the discriminant variables together with a constant.

**Table 4. Standardized and raw coefficients and constants for parameters of uric acid exchange, metabolism and neuroendocrine-immune complex**

| **Coefficients** | **Standardized** | | | **Raw** | | |
|---|---|---|---|---|---|---|
| **Variables** | Root 1 | Root 2 | Root 3 | Root 1 | Root 2 | Root 3 |
| **Uricosuria, mM/24 h** | 1,529 | -0,181 | 0,204 | 2,539 | -0,300 | 0,338 |
| **Uricemia, mM/L** | 1,003 | 0,485 | -0,520 | 13,85 | 6,694 | -7,174 |
| **Uricemia normalized, Z** | -0,332 | 0,345 | 0,943 | -0,355 | 0,368 | 1,007 |
| **PSD T4-δ, $\mu V^2$/Hz** | -0,133 | 0,091 | -0,116 | -0,0006 | 0,0004 | -0,0005 |
| **PSD O2-θ, %** | -0,356 | 0,042 | 0,501 | -0,094 | 0,011 | 0,132 |
| **Laterality δ, %** | -0,151 | -0,104 | 0,531 | -0,004 | -0,003 | 0,015 |
| **Calcitonin, ng/L** | -0,447 | 0,021 | -0,085 | -0,099 | 0,005 | -0,019 |
| **Phagocytose Index vs Staph. aur., %** | 0,497 | -0,395 | -0,065 | 0,422 | -0,336 | -0,056 |
| **Bacteriuria, points** | -0,210 | -0,858 | -0,427 | -0,865 | -3,527 | -1,758 |
| **PSD C4 Entropy** | 0,808 | 1,203 | -0,374 | 6,676 | 9,945 | -3,092 |
| **PSD F4 Entropy** | 0,028 | -0,886 | 0,319 | 0,179 | -5,678 | 2,041 |
| **Pan-Lymphocytes of Blood, %** | -1,371 | -0,464 | 0,032 | -0,179 | -0,061 | 0,004 |
| **Kerdö Vegetative Index, units** | 0,668 | 0,679 | 0,033 | 0,034 | 0,034 | 0,002 |
| **Bactericidity vs Staph. aur., $10^9$ Bac/L** | -0,660 | -0,395 | -0,341 | -0,027 | -0,016 | -0,014 |
| **IgA Saliva, mg/L** | -0,710 | -0,122 | -0,116 | -0,021 | -0,005 | -0,003 |
| **IgG Serum, g/L** | -0,346 | 0,012 | 0,073 | -0,094 | 0,003 | 0,020 |
| **PSD C3-δ, %** | 0,432 | 0,407 | -0,380 | 0,023 | 0,022 | -0,020 |
| **Popovych's Strain Index-1, points** | 0,022 | 0,214 | -0,186 | 0,206 | 1,981 | -1,722 |
| **AMo/MxDMn as SV balance Index** | -0,379 | -0,152 | -0,046 | -0,0017 | -0,0007 | -0,0002 |
| **Body Mass Index, kg/$m^2$** | 0,395 | 0,449 | 0,225 | 0,112 | 0,127 | 0,064 |
| **Magnesium Plasma, mM/L** | -0,139 | 0,282 | -0,518 | -3,728 | 7,560 | -13,86 |
| **Phosphates Plasma, mM/L** | -0,310 | -0,294 | -0,239 | -1,570 | -1,492 | -1,214 |
| **Potassium Plasma, mM/L** | -0,018 | -0,304 | -0,479 | -0,032 | -0,554 | -0,874 |
| **RMSSD, msec** | 0,435 | 0,549 | -0,342 | 0,025 | 0,032 | -0,020 |
| **Bifidobacteria faeces, lg CFU/g** | -0,426 | -0,4041 | 0,094 | -0,366 | -0,347 | 0,080 |
| **Entropy of Immunocytogram** | -0,169 | 0,372 | -0,341 | -6,341 | 13,94 | -12,77 |
| **Creatinine Plasma, µM/L** | -0,068 | 0,015 | -0,619 | -0,005 | 0,001 | -0,046 |
| **Creatininuria, mM/24 h** | -0,138 | 0,188 | -0,406 | -0,039 | 0,053 | -0,114 |
| | | | **Constants** | -37,08 | 14,51 | 42,59 |
| | | | **Eigenvalues** | 15,51 | 2,340 | 1,134 |
| | | **Cumulative Proportio** | | ,817 | ,940 | 1,000 |

At the next stage of the analysis, the actual values of the parameters were normalized and grouped into three discriminant roots based on the structural coefficients (Table 5). In addition to discriminant variables, the table also presents variables that are not included in the model, but are still informal carriers of identifying information.

**Table 5. Correlations of variables with canonical roots, root mean values and Z-values of parameters of uric acid exchange, metabolism and neuroendocrine-immune complex**

| Variables | Correlations Variables-Roots | | | S± E- III (30) | S2- E+ II (15) | S± E+ I (21) | S- E2+ IV (22) |
|---|---|---|---|---|---|---|---|
| ***Root 1 (81,7%)*** | **R 1** | **R 2** | **R 3** | **-4,42** | -1,17 | +1,43 | **+5,45** |
| **Uricosuria** | **0,583** | -0,309 | -0,016 | **-0,97** | +1,17 | +1,26 | **+3,87** |
| **Creatininuria** | **0,085** | 0,084 | -0,025 | **-1,30** | -1,15 | -0,52 | **-0,47** |
| **Entropy of Immunocytogram** | **0,045** | 0,013 | -0,076 | **-0,07** | +0,07 | +0,13 | **+0,13** |
| **Electrokinetic Index** | currently not in model | | | **-0,05** | +0,17 | +0,26 | **+0,73** |
| **IgG Serum** | **-0,029** | 0,047 | 0,046 | **+1,10** | +0,65 | +0,89 | **+0,64** |
| **Phagocytose Index vs St. aureus** | **-0,033** | 0,032 | -0,088 | **+0,40** | +0,39 | +0,39 | **+0,14** |
| **IgA Saliva** | **-0,075** | -0,014 | -0,088 | **-0,48** | -0,53 | -0,71 | **-1,15** |
| **Calcitonin** | **-0,027** | -0,044 | 0,107 | **-0,57** | -0,60 | -0,69 | **-0,87** |
| **$CD4^+CD3^+$ T-helper Lymphocyte** | currently not in model | | | **-2,12** | -2,21 | -2,93 | **-3,47** |
| **Age** | currently not in model | | | **+0,27** | +0,14 | -0,06 | **-0,40** |
| ***Root 2 (12,3%)*** | **R 1** | **R 2** | **R 3** | +0,11 | -2,26 | **+2,25** | -0,77 |
| **Uricemia** | 0,018 | **0,423** | 0,204 | -0,53 | -1,89 | **+0,09** | -0,70 |
| **PSD C4 Entropy** | -0,011 | **0,099** | 0,032 | -0,14 | -0,67 | **+0,07** | -0,44 |
| **Kerdö Vegetative Index** | -0,006 | **0,150** | -0,028 | 0,00 | -0,29 | **+0,29** | -0,18 |
| **Triiodothyronine** | currently not in model | | | -0,49 | -0,36 | **-0,06** | -0,67 |
| **Bactericidity vs Staph. aureus** | 0,008 | **0,114** | -0,035 | -1,06 | -1,43 | **-0,25** | -1,12 |
| **PSD T4-δ, $\mu V^2$/Hz** | -0,015 | **0,215** | -0,134 | +0,69 | +0,02 | **+2,60** | -0,35 |
| **PSD C3-δ, $\mu V^2$/Hz** | currently not in model | | | +0,70 | +1,80 | **+2,47** | -0,20 |
| **PSD F7-θ, $\mu V^2$/Hz** | currently not in model | | | +0,66 | +0,71 | **+1,59** | -0,16 |
| **PSD C3-δ, %** | -0,007 | **0,110** | -0,155 | +0,15 | +0,26 | **+0,83** | -0,14 |
| **PSD T4-δ, %** | currently not in model | | | +0,30 | -0,11 | **+0,78** | -0,33 |
| **AMo/MxDMn HRV** | 0,009 | **0,176** | -0,154 | -0,34 | -0,47 | **+1,63** | -0,07 |
| **Popovych's Strain Index-1** | 0,011 | **0,111** | -0,197 | +1,29 | +1,87 | **+3,83** | +1,28 |
| **Body Mass Index** | 0,028 | **0,117** | 0,040 | +0,83 | +0,52 | **+1,21** | +1,02 |
| **Magnesium Plasma** | 0,028 | **0,166** | -0,230 | -1,55 | -1,36 | **-0,87** | -1,47 |
| **Killing Index vs Staph. aureus** | currently not in model | | | -1,25 | -1,32 | **-0,70** | -1,12 |
| **Bacteriuria** | -0,008 | **-0,164** | -0,125 | +1,11 | +1,75 | **+0,93** | +1,17 |
| **Pan-Lymphocytes** | -0,002 | **-0,118** | 0,013 | +0,34 | +0,68 | **-0,05** | +0,40 |
| **PSD F4 Entropy** | -0,009 | **-0,106** | 0,115 | -0,38 | -0,44 | **-1,20** | -0,31 |
| **Phosphates Plasma** | -0,062 | **-0,101** | -0,052 | -0,69 | -0,53 | **-1,17** | -1,21 |
| **Glucose Plasma** | currently not in model | | | -0,01 | +0,32 | **-0,78** | -0,17 |
| ***Root 3 (6,0%)*** | **R 1** | **R 2** | **R 3** | +0,82 | **-1,64** | -0,92 | +0,89 |
| **Laterality δ, %** | -0,049 | 0,003 | **0,291** | +0,11 | **-0,75** | -0,69 | -0,30 |
| **PSD O2-θ, %** | -0,072 | -0,001 | **0,277** | +0,52 | **-0,45** | -0,44 | -0,18 |
| **PSD T6-α, %** | currently not in model | | | -0,43 | **-0,63** | -0,46 | +0,13 |
| **$CD8^+CD3^+$ T-cytolytic Lymphoc** | currently not in model | | | -0,06 | **-0,71** | -0,04 | +0,06 |
| **Bifidobacteria faeces** | 0,002 | 0,001 | **0,092** | -1,13 | **-1,35** | -1,27 | -1,09 |
| **Lactobacilli faeces** | currently not in model | | | -1,19 | **-1,35** | -1,24 | -1,12 |
| **$(Ca/K)^{0.5}$ Plasma** | currently not in model | | | +0,27 | **-0,23** | +0,01 | -0,01 |
| **Cortisol** | currently not in model | | | +0,75 | **+0,13** | +0,33 | +0,59 |
| **Leukocyturia** | currently not in model | | | +0,89 | **+0,39** | +0,51 | +0,88 |
| **Creatinine Plasma** | 0,012 | -0,002 | **-0,105** | +1,09 | **+1,38** | +1,33 | +1,18 |
| **Interleukin-1** | currently not in model | | | +0,09 | **+1,06** | +0,29 | +0,38 |
| **Testosterone** | currently not in model | | | +0,22 | **+1,03** | +0,55 | -0,12 |
| **Sex Index (M=2;F=1)** | currently not in model | | | -0,24 | **+0,39** | -0,02 | +0,11 |
| **Potassium Plasma** | 0,035 | -0,038 | **-0,148** | -1,55 | **-0,10** | -0,31 | -0,32 |
| **RMSSD HRV** | 0,021 | -0,070 | **-0,058** | -0,01 | **+0,38** | -0,31 | +0,23 |

The result of the analysis is the visualization of each patient in the information space of discriminant roots (Fig. 1).

The localization of members of the **S±E-** cluster in the extreme left zone of the axis of the first root reflects the combination of **hypouricosuria** with hypocreatininuria and normal, but **minimal** for the samples, levels of entropy of the immunocytogram and the electrokinetic index - on the one hand; and with **maximally** for the sample elevated levels of serum IgG and phagocytosis activity, minimally for the sample reduced levels of salivary IgA, T-helpers, and calcitonin, as well as the maximum average age of patients, on the other hand. At the opposite pole, members of the **S-E2+** cluster are located, in which pronounced **hyperuricosuria** is combined with the **maximum** for the sample levels of the parameters **inversely** related to the root, and the **minimum** for the sample levels of the parameters **directly** related to the root. In addition, the members of this cluster are on average the youngest in the sample.

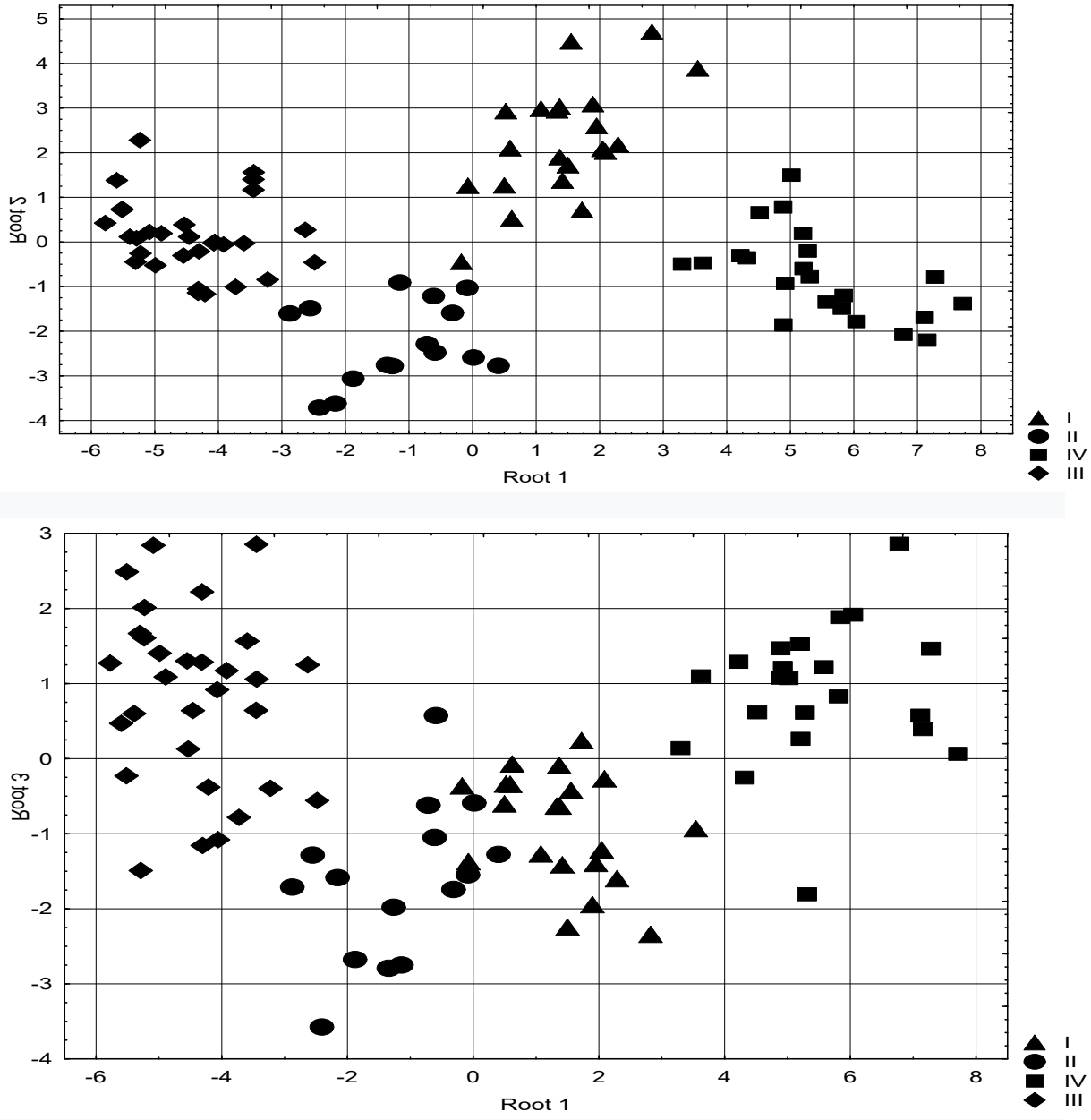



**Fig. 1a, 1b. Scattering of individual values of the first and second (top) and first and third (bottom) discriminant integral roots of patients from different clusters**

The members of the other two clusters occupy intermediate positions and are partially mixed, which reflects the absence of significant differences between the parameters of the mentioned constellation of parameters.

However, these clusters are clearly demarcated along the axis of the second root. At the same time, the top position (centroid: +2,25) is occupied by members of the **S±E+** cluster, which are characterized, firstly, by a normal, but **maximum** for the sample, level of **uricemia** in combination with such EEG entropy in the C4 locus, Kerdö autonomic index, triiodothyronine and bactericidal activity of blood neutrophils against Staphylococcus aureus; secondly, by the **maximally** increased PSD of the delta-rhythm in the T4 and C3 loci and theta-rhythm in the F7 locus, Baevsky's sympatho-vagal balance index and Popovych's strain index, as well as body mass index; thirdly, by minimally reduced levels of the killing index of Staphylococcus aureus and the plasma magnesium, that is, the **maximum** for the sample. On the other hand, the members of this cluster have **minimal** for the sample bacteriuria and a normal level of pan-lymphocytes, and maximally reduced levels of EEG entropy in the F4 locus, as well as phosphatemia and glycemia.

Additional demarcation of the members of the **S2-E+** cluster occurs along the axis of the third root, which reflects, firstly, their left lateralization of the delta-rhythm and **maximally reduced** PSD of the theta-rhythm in the O2 locus and alpha-rhythm in the T6 locus, the content of T-killers in the blood and favorable acidophilic microflora in feces; secondly, normal, but **minimal** for the sample levels of cortisolemia, Ca/K-marker of sympathetic-vagal balance and leukocyturia. On the other hand, among the members of this cluster, the **maximum** percentage of men and the **maximally** elevated plasma levels of testosterone, creatinine, and IL-1 and normal, but **maximal** for the sample, levels of plasma potassium and vagotonia.

The apparent clear demarcation of all four clusters is documented by the calculation of Mahalanobis distances (Table 6).

**Table 6. Squares of Mahalanobis distances between clusters, F-criterions (df=28,6) and p-levels**

| Clusters | S±E+ I | S2-E+ II | S-E2+ IV | S±E- III |
|---|---|---|---|---|
| S±E+ I (21) | 0 | 27,6 | 28,6 | 41,7 |
| S2-E+ II (15) | 5,9 $10^{-6}$ | 0 | 52,5 | 22,2 |
| S-E2+ IV (22) | 7,4 $10^{-6}$ | 11,3 $10^{-6}$ | 0 | 98,2 |
| S±E- III (30) | 12,5 $10^{-6}$ | 5,4 $10^{-6}$ | 30,2 $10^{-6}$ | 0 |

Another result of discriminant analysis is the possibility of retrospective identification of members of different clusters by calculating individual discriminant functions according to the coefficients and constants given in the table. 7.

**Table 7. Coefficients and constants for cluster classification functions**

| Clusters | S±E+ I | S2-E+ II | S-E2+ IV | S±E- III |
|---|---|---|---|---|
| *Variables* | p=,239 | p=,170 | p=,250 | p=,341 |
| Uricosuria, mM/24 h | 89,13 | 83,64 | 100,9 | 75,51 |
| Uricemia, mM/L | 194,2 | 133,3 | 216,8 | 86,54 |
| Uricemia normalized, Z | -62,88 | -64,34 | -63,60 | -59,85 |
| PSD T4-δ, $\mu V^2/Hz$ | -0,148 | -0,148 | -0,153 | -0,146 |
| PSD O2-θ, % | -6,565 | -6,466 | -6,739 | -5,808 |
| Laterality δ, % | 0,897 | 0,911 | 0,916 | 0,956 |

| | | | | |
|---|---|---|---|---|
| **Calcitonin, ng/L** | -1,975 | -1,723 | -2,423 | -1,435 |
| **Phagocytose Index vs Staph. aur., %** | 154,3 | 154,8 | 156,9 | 152,5 |
| **Bacteriuria, points** | 74,64 | 94,07 | 78,63 | 84,19 |
| **PSD C4 Entropy** | 160,1 | 100,1 | 151,4 | 94,44 |
| **PSD F4 Entropy** | -194,0 | -170,3 | -172,5 | -179,4 |
| **Pan-Lymphocytes of Blood, %** | -14,62 | -13,89 | -15,15 | -13,44 |
| **Kerdö Vegetative Index, units** | 2,699 | 2,457 | 2,734 | 2,433 |
| **Bactericidity vs Staph. aur., $10^9$ Bac/L** | -0,870 | -0,717 | -0,956 | -0,701 |
| **IgA Saliva, mg/L** | -1,785 | -1,713 | -1,864 | -1,663 |
| **IgG Serum, g/L** | -4,180 | -3,966 | -4,532 | -3,604 |
| **PSD C3-δ, %** | 1,097 | 0,954 | 1,089 | 0,882 |
| **Popovych's Strain Index-1, points** | -226,0 | -234,2 | -234,2 | -234,4 |
| **AMo/MxDMn as SV balance Index** | 0,108 | 0,116 | 0,103 | 0,119 |
| **Body Mass Index, $kg/m^2$** | 9,098 | 8,187 | 9,280 | 8,282 |
| **Magnesium Plasma, mM/L** | 211,3 | 196,9 | 148,4 | 192,9 |
| **Phosphates Plasma, mM/L** | 64,89 | 76,58 | 60,88 | 75,16 |
| **Potassium Plasma, mM/L** | -5,639 | -2,424 | -5,675 | -5,781 |
| **RMSSD, msec** | 3,845 | 3,651 | 3,815 | 3,597 |
| **Bifidobacteria faeces, lg CFU/g** | -5,063 | -2,605 | -5,345 | -2,042 |
| **Entropy of Immunocytogram** | 3460 | 3423 | 3369 | 3445 |
| **Creatinine Plasma, µM/L** | 4,455 | 4,497 | 4,348 | 4,403 |
| **Creatininuria, mM/24 h** | 6,295 | 6,240 | 5,773 | 6,211 |
| **Constants** | -9544 | -9545 | -9672 | -9291 |

Taking into account all features enables the retrospective recognition of members of all clusters almost without error: the classification accuracy is 98,9% (Table 8).

**Table 8. Classification matrix for clusters**

Rows: observed classifications; columns: predicted classifications

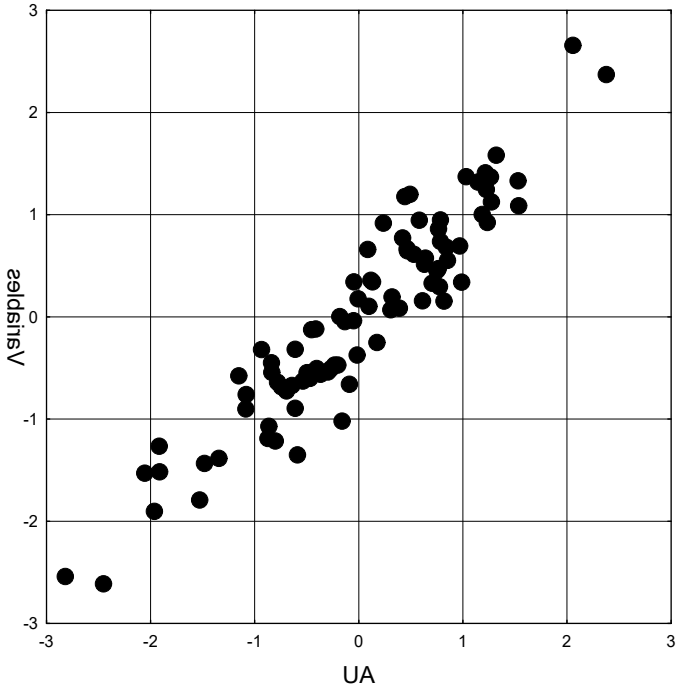
| | Percent | S±E+ I | S2-E+ II | S-E2+ IV | S±E- III |
|---|---|---|---|---|---|
| **Clusters** | correct | p=,239 | p=,170 | p=,250 | p=,341 |
| I | 95,2 | **20** | **1** | 0 | 0 |
| II | 100 | 0 | **15** | 0 | 0 |
| IV | 100 | 0 | 0 | **22** | 0 |
| III | 100 | 0 | 0 | 0 | **30** |
| Total | 98,9 | 20 | 16 | 22 | 30 |

In order to study the relationship between parameters of uric acid metabolism, on the one hand, and all other parameters registered in this study, a canonical correlation analysis procedure was performed. The program selects two almost equal pairs of canonical roots. The uric acid root of the first pair represents, mainly, uricosuria, while actual and normalized uricemia give significantly smaller and opposite factor loads on the root (Table 9). The factor structure of the resulting root is represented, almost entirely, by parameters that are subject to upregulation by uricosuria. These are 4 HRV-markers of vagal tone, EEG entropy in the F7 and F8 loci, PSD of alpha-rhythm in the F7 locus and theta-rhythm in the T5 locus, as well as metabolic parameters: excretion of urea, chloride, sodium and creatinine as well as lithogenicity of urine. On the other hand, beta-rhythm PSD in the T6 locus was subject to upregulation by uricemia, and in the F7 locus - to downregulation by uricosuria.

**Table 9. Factor structure of the first pair of canonical roots of parameters of uric acid exchange (left set) and neuro-endocrine, metabolic and immune parameters (right set)**

| *Left set* | *Root 1* |
|---|---|
| **Uricosuria, mM/24 h** | **-0,886** |
| **Uricemia, mM/L** | **0,493** |
| **Uricemia normalized, Z-score** | **0,472** |
| ***Right set*** | **Root 1** |
| **LF Power HRV, msec$^2$** | **-0,466** |
| **LF Power HRV, %** | **-0,411** |
| **MxDMn HRV as Vagal tone** | **-0,268** |
| **VLF Power HRV, msec$^2$** | **-0,244** |
| **PSD F7 Entropy** | **-0,231** |
| **PSD F8 Entropy** | **-0,170** |
| **PSD F8-α, %** | **-0,251** |
| **PSD T5-θ, %** | **-0,162** |
| **PSD T6-β, μV$^2$/Hz** | **0,216** |
| **PSD F7-β, μV$^2$/Hz** | **0,196** |
| **Urea Excretion, mM/24 h** | **-0,603** |
| **(Cau•UAu/Mgu•Cru)$^{0,25}$ as Urolithogenicity, un** | **-0,404** |
| **Chloride Excretion, mM/24 h** | **-0,317** |
| **Sodium Excretion, mM/24 h** | **-0,319** |
| **Creatininuria, mM/24 h** | **-0,309** |

In general, uric acid determines this constellation of parameters by 88% (Fig. 2).




R=0,940; $R^2$=0,883; $\chi^2_{(117)}$=293; p<$10^{-6}$; Lambda Prime=0,011

**Fig. 2. Scatterplot of the canonical correlation between parameters of uric acid exchange (line X) and neural and metabolic parameters (line Y). The first pair of roots**

Instead, the uric acid root of the second pair is mainly represented by uricemia, both actual (to a greater extent) and normalized (to a lesser extent). Uricosuria gives a smaller factor load on the root, but unidirectional, which simplifies the interpretation of uric acid determination of parameters, information about which is condensed in the resulting canonical root.

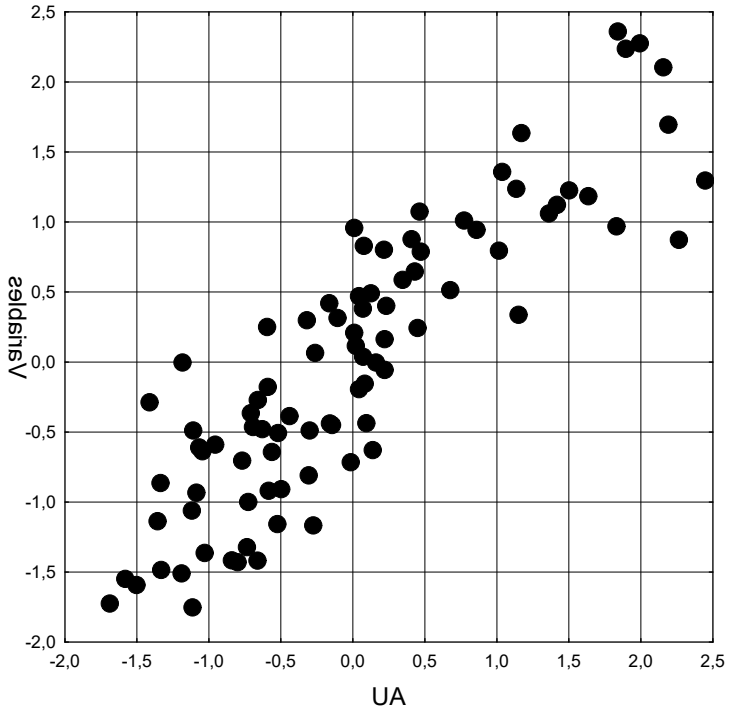
Downregulation of 7 EEG parameters, 3 HRV-markers of vagal tone and triiodothyronine level was revealed by uric acid, instead of upregulation of 4 EEG parameters and HRV-marker of sympatho-vagal balance. Such a neuro-endocrine pattern is accompanied by

downregulation of the relative levels of T-helpers and polymorphonuclear neutrophils in the blood, the concentration of IgG in saliva, and the content of Escherichia coli with weakened enzymatic activity in feces, instead by a upregulation of the completion of phagocytosis by blood neutrophils of representatives of gram-positive and gram-negative microbes, the relative level of lymphocytes in the blood in general and the population of natural killers in particular, as well as the entropy of the immunocytogram. The metabolic effects of uric acid are manifested by a positive effect on the excretion of urea, chloride and sodium, the lithogenicity of urine, the plasma levels of creatinine and calcium, but a negative effect on glycemia.

**Table 10. Factor structure of the second pair of canonical roots of parameters of uric acid exchange (left set) and neuro-endocrine, immune and metabolic parameters (right set)**

| *Left set* | Root 2 |
|---|---|
| Uricemia, mM/L | -0,689 |
| Uricosuria, mM/24 h | -0,382 |
| Uricemia normalized, Z-score | -0,283 |
| *Right set* | Root 2 |
| PSD P4-δ, % | 0,389 |
| PSD T5-θ, % | 0,333 |
| PSD P3-δ, % | 0,324 |
| PSD C3-θ, $\mu V^2/Hz$ | 0,312 |
| PSD F7 Entropy | 0,303 |
| PSD F8 Entropy | 0,300 |
| Index β, % | 0,221 |
| MxDMn HRV as Vagal tone | 0,383 |
| VLF Power HRV, $msec^2$ | 0,374 |
| LF Power HRV, $msec^2$ | 0,292 |
| Triiodothyronine, nM/L | 0,315 |
| PSD T4-β, % | -0,394 |
| PSD F4-β, % | -0,386 |
| PSD T3-β, % | -0,281 |
| PSD P3-α, % | -0,266 |
| Baevski Stress Index HRV, ln units | -0,192 |
| $CD4^+CD3^+$ T-helper Lymphocytes, % | 0,673 |
| IgG Saliva, mg/L | 0,653 |
| Polymorphonucleary Neutrophils of Blood, % | 0,499 |
| *E. coli attenuated* faeces, % | 0,496 |
| $CD56^+$ Natural Killer Lymphocytes, % | -0,542 |
| Killing Index vs E. coli, % | -0,476 |
| Killing Index vs Staph. aureus, % | -0,446 |
| Pan-Lymphocytes of Blood, % | -0,436 |
| Entropy of Immunocytogram | -0,425 |
| Urea Excretion, mM/24 h | -0,475 |
| Creatinine Plasma, µM/L | -0,464 |
| $(Cau•UAu/Mgu•Cru)^{0,25}$ as Urolithogenicity, uns | -0,408 |
| Calcium Plasma, mM/L | -0,259 |
| Chloride Excretion, mM/24 h | -0,252 |
| Sodium Excretion, mM/24 h | -0,252 |
| Glucose Plasma, mM/L | 0,275 |

This constellation of parameters is determined by uric acid by 77% (Fig. 3).




R=0,878; $R^2$=0,771; $\chi^2_{(76)}$=152; $p<10^{-6}$; Lambda Prime=0,098

**Fig. 3. Scatterplot of the canonical correlation between parameters of uric acid exchange (line X) and neuroendocrine, immune and metabolic parameters (line Y). The second pair of roots**

The influence of uric acid on the registered parameters is even more noticeable when analyzing the relationships between **individual changes** in parameters as a result of adaptogenic balneotherapy.

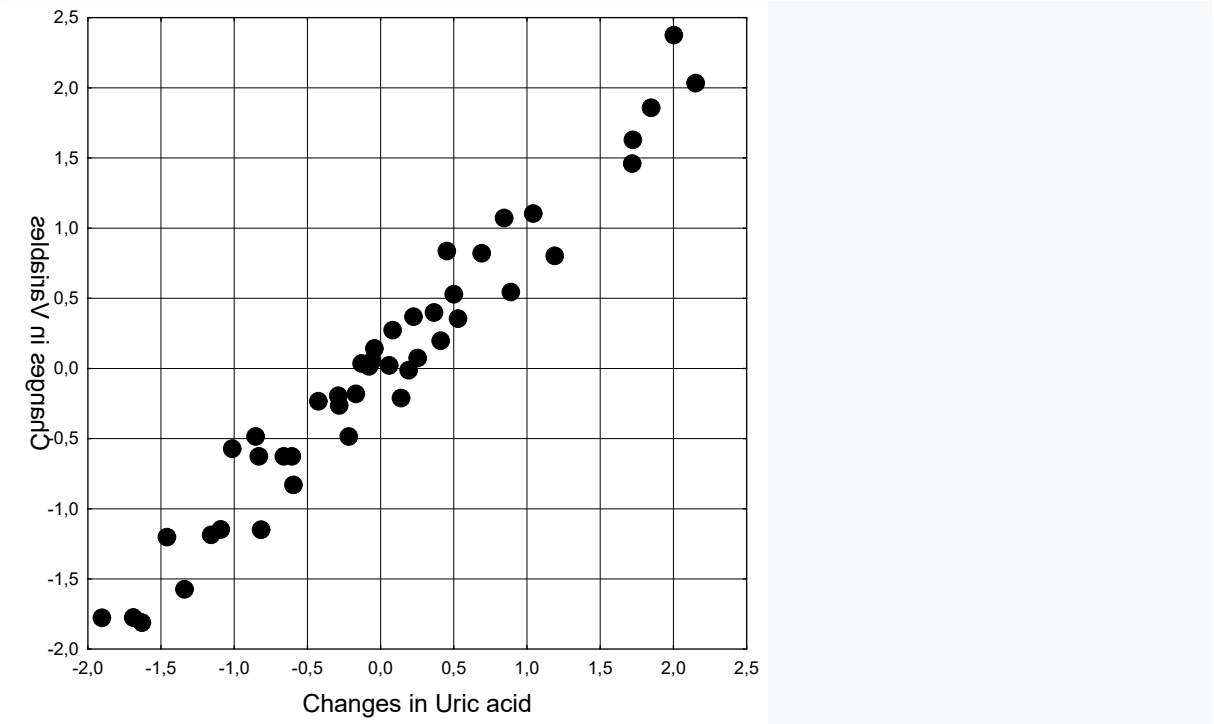
A canonical correlation analysis conducted using a similar algorithm also revealed two pairs of canonical roots. The first pair demonstrates that the dynamics of uricosuria and uricemia positively determine the dynamics of, first, the PSD of theta-rhythm in the T3 locus and beta-rhythm in the O2 locus as well as HRV-markers of vagal tone and sympatho-vagal balance; secondly, of diuresis and excretion of urea, magnesium, sodium, phosphates, calcium, potassium and chloride, as well as calcemia and magnesiumemia; thirdly, of serum IgG and CIC. Instead, changes in cortisolemia and testosteroneemia as well as TNF-alpha and the intensity of Staph. aureus phagocytosis are subject to negative determination (Table 11).

**Table 11. Factor structure of the first pair of canonical roots of changes in parameters of uric acid exchange (left set) and neuro-endocrine, metabolic and immune parameters (right set)**

| ***Left set*** | **Root 1** |
|---|---|
| **Uricosuria, mM/24 h** | **-0,835** |
| **Uricemia, mM/L** | **-0,539** |
| ***Right set*** | **Root 1** |
| **PSD T3-θ, %** | **-0,332** |
| **PSD O2-β, %** | **-0,289** |
| **LF/HF as Sympatho/Vagal balance** | **-0,218** |
| **RMSSD HRV, msec** | **-0,213** |
| **$(Cap•Pu/Pp•Cau)^{0,25}$ as Parathyroid activity** | **-0,186** |
| **Cortisol, nM/L** | **0,270** |
| **Testosterone, nM/L** | **0,139** |
| **Diurese, L/24 h** | **-0,664** |
| **Urea Excretion, mM/24 h** | **-0,630** |

| | |
|---|---|
| **Magnesium Excretion, mM/24 h** | **-0,307** |
| **Sodium Excretion, mM/24 h** | **-0,247** |
| **Phosphates Excretion, mM/24 h** | **-0,213** |
| **Calcium Excretion, mM/24 h** | **-0,194** |
| **Potassium Excretion, mM/24 h** | **-0,189** |
| **Chloride Excretion, mM/24 h** | **-0,143** |
| **Calcium Plasma, mM/L** | **-0,211** |
| **Magnesium Plasma, mM/L** | **-0,122** |
| **IgG Serum, g/L** | **-0,266** |
| **Circulating Immune Complicis, units** | **-0,201** |
| **Microbian Count vs Staph. aur., Bact/Phagocyte** | **0,263** |
| **TNF-alpha, ng/L** | **0,106** |

The dynamics of such a constellation of parameters is determined by the dynamics of uric acid by 96% (Fig. 4).




$R=0,978$; $R^2=0,956$; $\chi^2_{(76)}=135$; $p<10^{-4}$; Lambda Prime=0,003

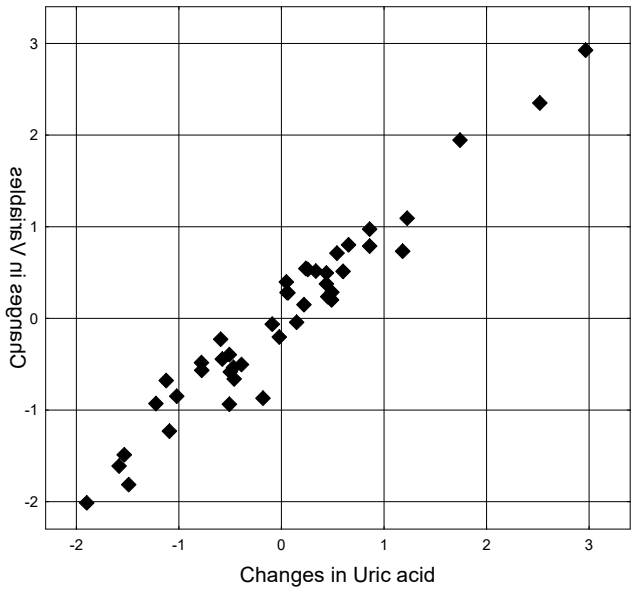
**Fig. 4. Scatterplot of the canonical correlation between changes in uricosuria and uricemia (line X) and neuro-endocrine, metabolic, and immune parameters (line Y). The first pair of roots**

The factor structure of the second pair of roots is heterogeneous, therefore more difficult to interpret (Table 12). The dynamics of uricemia - the major element of the uric acid root - negatively determines the PSD dynamics of the beta-rhythm in 5 loci and the alpha-rhythm in the T5 locus, as well as calcitonin and T-helpers. Instead, the PSD of the delta-rhythm in the T5 locus, the alpha-rhythm in the P4 and P3 loci, electrolyte markers of sympatho-vagal balance and parathyroid activity, levels in the blood of chloride, sodium, calcium and magnesium, as well as monocytes and CIC are subject to upregulation.

The dynamics of uricosuria - a minor element of the uric acid root - negatively determines the dynamics of the alpha-rhythm index and testosteroneemia, but positively – HRV-markers of vagal tone and sympatho-vagal balance, as well as diuresis and excretion of urea, magnesium, phosphates, calcium, and potassium.

**Table 12. Factor structure of the second pair of roots of changes in parameters of UA exchange (left set) and neuro-endocrine, metabolic and immune parameters (right set)**

| *Left set* | Root 2 |
|---|---|
| Uricemia, mM/L | -0,842 |
| Uricosuria, mM/24 h | 0,550 |
| *Right set* | Root 2 |
| PSD P4-β, % | 0,588 |
| PSD P3-β, % | 0,553 |
| PSD T6-β, % | 0,473 |
| PSD C4-β, % | 0,402 |
| PSD C3-β, % | 0,363 |
| PSD T5-α, % | 0,268 |
| Calcitonin, ng/L | 0,251 |
| $CD4^+CD3^+$ T-helper Lymphocytes, % | 0,612 |
| PSD T5-δ, % | -0,308 |
| PSD P4-α, $\mu V^2/Hz$ | -0,305 |
| PSD P3-α, $\mu V^2/Hz$ | -0,252 |
| $(Ca/K)^{0,5}$ Plasma as Sympatho/Vagal balance | -0,308 |
| $(Cap•Pu/Pp•Cau)^{0,25}$ as Parathyroid activity | -0,168 |
| Chloride Plasma, mM/L | -0,276 |
| Sodium Plasma, mM/L | -0,276 |
| Calcium Plasma, mM/L | -0,201 |
| Magnesium Plasma, mM/L | -0,136 |
| Monocytes of Blood, % | -0,309 |
| Circulating Immune Complicis, units | -0,238 |
| Index α, % | -0,325 |
| Testosterone, nM/L | -0,159 |
| LF/HF as Sympatho/Vagal balance | 0,170 |
| RMSSD HRV, msec | 0,163 |
| Urea Excretion, mM/24 h | 0,474 |
| Diurese, L/24 h | 0,462 |
| Calcium Excretion, mM/24 h | 0,372 |
| Phosphates Excretion, mM/24 h | 0,319 |
| Magnesium Excretion, mM/24 h | 0,245 |
| Potassium Plasma, mM/L | 0,175 |




R=0,971; $R^2$=0,943; $\chi^2_{(37)}$=65; p=0,0033; Lambda Prime=0,057

**Fig. 5. Scatterplot of the canonical correlation between changes in UA (line X) and neuro-endocrine, metabolic, and immune parameters (line Y). The second pair of roots**

In general, uric acid determination of the dynamics of the listed parameters is 94% (Fig. 5).

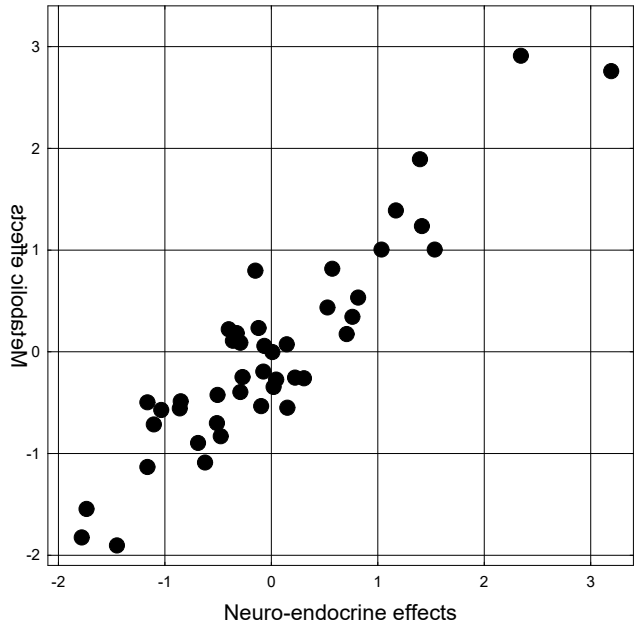
In conclusion, we will analyze neuroendocrine-metabolic and neuroendocrine-immune interrelationships. It was found that the dynamics of neuroendocrine parameters determines the dynamics of metabolic parameters by 85% (Tables 13 and 14, Fig. 6).

**Table 13. Factor structure of canonical roots of changes in neuroendocrine (left set) and metabolic (right set) parameters**

| Left set | R |
|---|---|
| PSD O2-β, % | 0,655 |
| PSD T6-β, % | 0,633 |
| PSD P4-β, % | 0,614 |
| PSD C4-β, % | 0,472 |
| PSD C3-β, % | 0,409 |
| PSD T3-θ, % | 0,357 |
| PSD P3-β, % | 0,312 |
| PSD T5-α, % | 0,518 |
| Calcitonin, ng/L | 0,249 |
| LF/HF as Sympatho/Vagal balance | 0,204 |
| PSD P4-α, $\mu V^2$/Hz | -0,602 |
| PSD P3-α, $\mu V^2$/Hz | -0,520 |
| Index α, % | -0,599 |
| PSD T5-δ, % | -0,536 |
| Cortisol, nM/L | -0,391 |
| Testosterone, nM/L | -0,175 |
| **Right set** | **R** |
| Calcium Excretion, mM/24 h | 0,774 |
| Diurese, L/24 h | 0,461 |
| Phosphates Excretion, mM/24 h | 0,441 |
| Magnesium Excretion, mM/24 h | 0,387 |
| Urea Excretion, mM/24 h | 0,187 |
| Potassium Plasma, mM/L | 0,578 |
| Magnesium Plasma, mM/L | -0,540 |
| Chloride Excretion, mM/24 h | -0,295 |
| Sodium Excretion, mM/24 h | -0,334 |

**Table 14. Correlation matrix for changes in neuroendocrine and metabolic parameters**

| variable | Correlations, left set with right set | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Urea E | Mg | K | Diur | Ca Ex | P Ex | Mg Ex | Cl Ex | Na Ex |
| Cortisol | -0,12 | 0,21 | -0,37 | -0,12 | -0,29 | -0,08 | -0,11 | 0,18 | 0,17 |
| Calcitonin | -0,13 | -0,06 | 0,32 | -0,06 | 0,03 | 0,08 | -0,11 | -0,42 | -0,39 |
| Testosterone | -0,06 | 0,22 | 0,06 | -0,11 | -0,19 | -0,44 | -0,05 | 0,14 | 0,13 |
| LF/HF | 0,34 | -0,25 | 0,11 | 0,24 | 0,17 | 0,01 | 0,30 | 0,04 | 0,05 |
| Index Alpha | -0,07 | 0,53 | -0,19 | -0,19 | -0,51 | -0,36 | -0,27 | 0,20 | 0,21 |
| T3T% | 0,25 | -0,00 | 0,10 | 0,42 | 0,26 | 0,04 | 0,20 | 0,19 | 0,19 |
| T5A% | 0,01 | -0,49 | 0,36 | -0,05 | 0,44 | 0,02 | 0,05 | -0,15 | -0,30 |
| T5D% | -0,08 | 0,43 | -0,36 | -0,06 | -0,41 | 0,01 | -0,07 | 0,11 | 0,23 |
| C3B% | 0,08 | -0,32 | 0,21 | 0,17 | 0,20 | 0,01 | 0,15 | -0,06 | -0,08 |
| C4B% | 0,17 | -0,28 | 0,20 | 0,28 | 0,25 | 0,03 | 0,30 | -0,09 | -0,11 |
| T6B% | 0,11 | -0,47 | 0,28 | 0,24 | 0,42 | 0,15 | 0,32 | -0,10 | -0,15 |
| P3B% | 0,13 | -0,21 | 0,15 | 0,15 | 0,29 | 0,09 | 0,22 | 0,04 | 0,01 |
| P3A | -0,06 | 0,43 | -0,20 | -0,11 | -0,46 | -0,28 | -0,21 | 0,22 | 0,27 |
| P4B% | 0,19 | -0,29 | 0,38 | 0,33 | 0,33 | 0,21 | 0,25 | -0,17 | -0,19 |
| P4A | -0,04 | 0,41 | -0,28 | -0,12 | -0,53 | -0,35 | -0,37 | 0,23 | 0,28 |
| O2B% | 0,01 | -0,36 | 0,27 | 0,31 | 0,35 | 0,09 | 0,13 | -0,08 | -0,09 |




R=0,921; $R^2$=0,848; $\chi^2_{(153)}$=183; p=0,047; Lambda Prime=0,002

**Fig. 6. Scatterplot of canonical correlation between changes in neuroendocrine (line X) and metabolic (line Y) parameters**

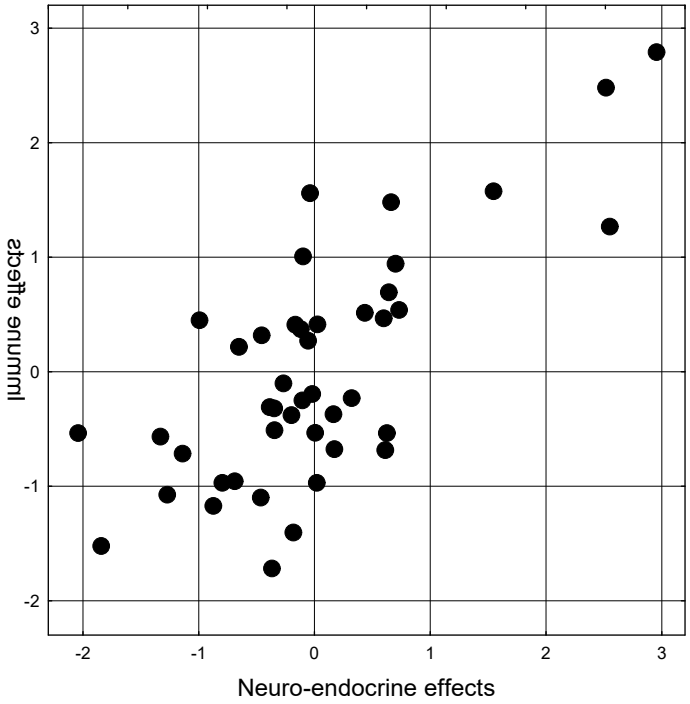
Neuroendocrine determination of immunity parameters is 54% (Tables 15 and 16, Fig. 7).

**Table 15. Factor structure of canonical roots of changes in neuroendocrine (left set) and immune (right set) parameters**

| Left set | R |
|---|---|
| Calcitonin, ng/L | 0,785 |
| RMSSD HRV, msec | 0,327 |
| PSD P4-β, % | 0,542 |
| PSD P3-β, % | 0,393 |
| PSD T6-β, % | 0,333 |
| PSD C4-β, % | 0,272 |
| PSD C3-β, % | 0,256 |
| PSD P4-α, $\mu V^2/Hz$ | -0,402 |
| **Right set** | **R** |
| Circulating Immune Complicis, units | -0,507 |
| Microbian Count vs Staph. aur., Bact/Phag | -0,213 |
| $CD4^+CD3^+$ T-helper Lymphocytes, % | 0,677 |
| TNF-alpha, ng/L | 0,393 |
| Monocytes of Blood, % | 0,124 |

**Table 16. Correlation matrix for changes in neuroendocrine and immune parameters**

| Root | Correlations, left set with right set | | | | |
|---|---|---|---|---|---|
| Removed | TNFa | MC Sa | Mon | TH | CIC |
| Calcitonin | 0,33 | -0,02 | 0,08 | 0,25 | -0,44 |
| RMSSD | 0,11 | -0,35 | 0,23 | 0,20 | 0,12 |
| C3B% | 0,10 | 0,08 | 0,08 | 0,14 | -0,14 |
| C4B% | 0,18 | -0,00 | 0,04 | 0,24 | 0,04 |
| T6B% | 0,27 | 0,03 | -0,01 | 0,13 | -0,12 |
| P3B% | 0,02 | -0,02 | -0,11 | 0,26 | -0,17 |
| P4B% | 0,21 | 0,01 | 0,07 | 0,32 | -0,17 |
| P4A | -0,14 | -0,00 | -0,07 | -0,32 | 0,04 |




R=0,735; $R^2$=0,540; $\chi^2_{(40)}$=57; p=0,040; Lambda Prime=0,205

**Fig. 7. Scatterplot of canonical correlation between changes in neuro-endocrine (line X) and immune (line Y) parameters**

## DISCUSSION

Therefore, within the framework of the "Physiological activity of uric acid" project, we demonstrated that despite the wide variability of uricemia and uricosuria both in healthy rats and in patients of the Truskavets resort with chronic pyelonephritis against the background of maladaptation, both parameters of uric acid metabolism are significantly correlated with EEG, HRV, hormones of adaptation, immunity, as well as exchange of electrolytes, creatinine, urea and glucose parameters.

Moreover, in another study within the framework of the next project, we found a correlation (r=-0,415) of uricemia with the level of reactive anxiety in postmenopausal women [6]. Li S. et al. [35] found that prevalence of hyperuricemia and increased serum uric acid levels were higher in the manic group (62,1%) than in the depressive (34,3%) or euthymia group (17,0%) (p<0,001); additionally, the severity of mania was positively correlated with the uric acid level (r=0,410, p<0,001). Young IK et al [60] found that the bipolar disorder group showed higher scores on the Young Mania Rating Scale (YMRS). Patients in their manic episodes showed higher plasma uric acid levels (4,9±1,3 mg/dL) than healthy control subjects (4,2±0,9 mg/dL; p<0,05). Uric acid levels showed correlation with severity of manic symptoms as assessed using the YMRS in all participants (ρ=0,28, p<0,05).

In Ortiz's R. et al [40] excellent review, conflicting data are collected. Elevated uric acid levels have been observed in acute mania. In addition, these levels were positively correlated with symptom severity and with the improvement of manic symptoms in diverse studies. Plasma uric acid levels were found to be higher in bipolar disorders (BD) patients than controls. As a result of these findings, testing for uric acid levels has been proposed as a screening test in acute mania. Uric acid levels have also been correlated with specific character traits including drive and disinhibition, both of which are common in mania. However, at least one study found no differences in uric acid levels between BD subjects and healthy controls. Uric acid, as one of a cluster of urinary metabolites, was correlated with first

depressive episode in drug-naïve mood disorders disease (MDD) subjects. Another study compared healthy controls and MDD patients and found that lower levels of uric acid were associated with MDD; indeed, the authors noted a strong inverse relation between Hamilton Depression Rating Scale (HDRS) scores and uric acid levels after 12 weeks of antidepressant treatment. Interestingly, in another study, subjects with MDD showed lower plasma uric acid levels than healthy controls and BD patients. A smaller study also found that lower levels of uric acid were associated with MDD compared to other psychiatric conditions; these normalized after five weeks of antidepressant treatment, though no significant differences were observed between those with depressive and anxiety disorders.

Fully aware that correlational relationships do not necessarily reflect functional relationships, we nevertheless take responsibility for asserting that (psycho)neurotropic, immunotropic, hormonal, and metabolic activity of the uric acid molecule has been established in our study. Additional evidence in favor of such a statement is the fact that correlations between balneotherapy-induced parameter **changes** were more numerous and generally stronger than in the **entire sample**. But the main argument should be considered the structural similarity of the molecules of uric acid (**2,6,8**-tri**oxipurine**) and adenosine [(2R,3R,4R,5R)-2-(6-amino**purine**-il)-5-(hydroximethyl) oxolan-3,4-diol)], and especially its antagonists such as theophylline (**2,6**-di**oxi**-1,3-dimethyl**purine** or 1,3-dimethyl**xantine**), caffeine (**2,6**-di**oxi**-1,3,7-trimethyl**purine** or 1,3,7-trimethyl**xantine**) and other methylxanthines.

The ubiquitous signaling nucleoside molecule, adenosine is found in different cells of the human body to provide its numerous physio/pharmacological role. The associated actions of endogenous adenosine are largely dependent on conformational change of the widely expressed heterodimeric G-protein-coupled A1, A2A, A2B, and A3 adenosine receptors. These receptors are well conserved on the surface of specific cells, where potent neuromodulatory properties of this bioactive molecule reflected by its easy passage through the rigid blood-brainbarrier, to simultaneously act on the central nervous system. The minimal concentration of adenosine in body fluids (30-300 nM) is adequate to exert its neuromodulatory action in the CNS [8,9,24,37]. Its physiological importance depends on the affinity of these receptors and the extracellular concentrations reached. Adenosine has been traditionally considered an **inhibitor of neuronal activity** and a regulator of cerebral blood flow [24]. In the only one found by us on the PubMed resource article, that is similar to our work [60], the bipolar disorder group showed **decreased** relative delta and alpha activity in the fronto-temporo-occipital region compared to the control group ($p<0,05$). However relative beta in Fp1 (frontopolar), Cz (central mid-line), and Pz (parietal mid-line) and relative gamma in Fp1 were **increased** in the bipolar disorder group, relative to the control group ($p<0,05$). The relative beta ($\rho=0,47$, $p<0,05$) and gamma ($\rho=0,41$, $p<0,05$) in Fp1 electrodes showed positive correlation with the YMRS scores. Authors concluded that adenosinergic transmission dysfunction may lead to occurrence of manic symptoms, considering that a key role of central nervous system adenosinergic receptors is to inhibit the release of various neurotransmitters and limit neuronal excitability. In addition, QEEG appeared to indicate excitatory neuro-modulation in manic patients.

In contrast to bipolar disorder patients with an elevated level of uricemia, the vast majority of the cohort we observed was characterized by hypouricemia, a minority had a normal level of uric acid, and only 5 had an elevated level. And precisely in the members of the cluster with normouricemia, significantly increased delta activity in the T4 and C3 loci and theta activity in the F7 locus were found. When analyzing the individual effects of balneotherapy, we agree with Jamwal S. et al. [24] stated a diffuse **inhibitory** effect of uric acid on beta- and alpha-rhythm-generating neurons of the CNS, but at the same time uric acid exerted an **activating** effect on neurons that generate delta- and theta-rhythms.

The figures presented by Winkelmann T. et al [59] give us reason to assume that the loci C3/C4 projected precentral gyrus, T3/T4 – inferior temporal gyrus, T5/T6 – transverse temporal cortex, P3/P4 – supramarginal gyrus. The **thickness** of these cortical structures is positively correlated with the HF HRV as marker of vagal tone. We found an inhibitory effect of uric acid on beta-rhythm generating neurons that project to loci P3 (r=-0,58), P4 (r=-0,51), T4 (r=-0,53), T3 (r=-0,43), T6 (r=-0,42), C4 (r=-0,32), and C3 (r=-0,31). Montenegro R.A. et al. [36] assessed the effects of anodal direct current stimulation over the T3 scalp position (aims to reach the insular cortex) on measures of cardiac autonomic control. The authors found that the parasympathetic activity (HF(log)) increased and the sympathetic activity (LF(log)) and sympatho-vagal balance (LF/HF(log)) decreased in athletes but not in untrained individuals. No significant changes in HRV indexes were provoked by sham stimulation in both groups. The authors attributed the specific results to neuroanatomical and functional changes in the brain induced by long-term exercise training. Furthermore, Piccirillo G. et al [41] demonstrated that anodal tDCS over T3 scalp position reduced sinus sympathetic activity and increased vagal sinus activity and baroreflex sensitivity in older, but not younger individuals.

This is in excellent agreement with our data on negative relationships of uric acid with HRV-markers of vagal tone (MxDMn: -0,37; TNN: -0,35; SDNN: -0,31) and positive with HRV-markers of sympathetic tone (AMo: 0,32; Stress Index: 0,34), which indicates the ability of uric acid to influence the brainstem and subcortical autonomous nuclei [2,52]. Such influence is more likely to be exerted precisely through the cortical nuclei [47,50], although the possibility of direct influence of uric acid on autonomous nuclei (NA, DMV, RVLM, locus coeruleus) should not be excluded

Adenosine receptors express also virtually all populations of immunocytes such as T, NK, B lymphocytes, macrophages, neutrophils, dendritic and endothelial cells [1,21,22,38,58]. Therefore, the possibility of a direct effect of uric acid on these immunocytes seems quite obvious. At the same time, the implementation of the immunotropic effects of uric acid through the central and autonomic nervous systems is no less likely.

**Table 17. Agreed and divergent propositions of the immunological homunculus**

| EEG and Immune Variables | EEG and Immune response | EEG and Immune Variables | EEG and Immune response |
|---|---|---|---|
| Tracey's hypothesis | | Tracey's hypothesis | |
| Activation of memory B cells | | Late cytokine release | |
| Fp2-θ PSDr | -0,26±0,12 | P4-δ PSDr | +0,34±0,17 |
| IgM | -0,39±0,22 | P4-β PSDr | -0,34±0,12 |
| IgA | -0,24±0,14 | O2-β PSDr | -0,33±0,13 |
| | | Interleukin-1 | -0,42±0,27 |
| | | C-reactive Protein | -0,26±0,06 |
| Tracey's hypothesis | | Popovych's hypothesis | |
| T cells regulation | | T cells regulation? | |
| T6-β PSDr | -0,25±0,12 | Fp2-δ PSDa | +3,13±1,56 |
| $CD3^+CD25^+$ T-regulatory Lym | +0,51±0,19 | Fp1-δ PSDa | +3,14±1,59 |
| $CD3^+CD8^+$ T-cytolytic Lymph | +0,60±0,26 | F3-δ PSDa | +2,53±1,34 |
| Popovych's hypothesis | | F8-δ PSDa | +7,62±3,11 |
| Activation of Phagocytosis? | | F7-α PSDr | +0,29±0,12 |
| O2-δ PSDr | +0,42±0,17 | F8 PSD Entropy | -0,46±0,21 |
| Microbial Count vs E. coli | +0,40±0,17 | $CD3^+CD25^+$T-regulatory | +0,51±0,19 |
| Microbial Count vs St. aureus | +0,39±0,13 | $CD3^+CD8^+$T-cytolytic | +0,60±0,26 |
| Killing Index vs Staph. aureus | +0,79±0,20 | | |
| Killing Index vs E. coli | +0,65±0,12 | | |
| Bactericidity vs E. coli | +1,64±0,39 | | |
| Bactericidity vs Staph. aureus | +1,54±0,42 | | |
| CIC | +0,43±0,13 | | |

According to the Tracey K.J. [56], there is a structured, somatotopically organized neural network that controls specific components of the immune response through input and output communication. Such a theoretical organization is similar to the classical homunculus, which demonstrates that certain areas of the brain control certain parts of the body, and in the future it will be possible to build an "immunological homunculus". Under the influence of this hypothesis, our laboratory conducted research to test it [26-29,45,48,49].

As can be seen from the comparative Table 17, in the presumed cortical *Center of B-cell of memory activation*, inhibition of the activity of generating θ-rhythm neurons is accompanied by a decrease in the content of immunoglobulins M and A in the blood. *Center for Late Cytokine Release*, by Tracey K.J. [56], is projected between the parietal and occipital loci. This is consistent with our data on the association of decreased IL-1 and C-reactive protein levels with inhibition of β-rhythm generating neurons in the O2 and P4 loci, simultaneously with activation of δ-rhythm generating neurons localized there. If we assume that the cortical *Center of T-lymphocyte regulation* is projected onto the T6 locus, it turns out that it has an inhibitory effect on the level of T-regulatory and T-cytolytic lymphocytes in the blood. At the same time, the data obtained by us provide grounds for putting forward an alternative hypothesis regarding the upregulation of T-lymphocytes by neurons generating δ- and α-rhythms, which are projected onto prefrontal loci. Finally, our modest contribution to the concept of the immunological homunculus is a hypothesis about localization in the right occipital part of the cerebral cortex of δ-rhythm generating neurons responsible for the *regulation of phagocytosis*.

The effect of uric acid on the plasma levels of cortisol, testosterone and calcitonin is carried out, presumably, through mediators of both neurons (ACh, NA, GABA, ACTH, LH, etc.) and immunocytes (cytokines, ACTH, etc.) within the framework of a triune neuro-endocrine-immune complex [45,46], as well as through adenosine receptors of endocrinocytes.

Finally, the effects of uric acid on electrolyte exchange are most likely mediated by its effects on the aforementioned hormones.

Our data confirms and develops both old [23,55] and modern [10,37] hypotheses about the physiological activity of uric acid.

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## ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all parent of participants the informed consent is got and used all measures for providing of anonymity of participants.

For all authors any conflict of interests is absent.

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