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Metabolic accompaniments of variants of uric acid exchange

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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 autonomic nervous, endocrine, and immune systems, the levels of which correlate with uricemia and/or uricosuria. The **aim** of this study is to clarify the relationship between parameters of exchange of uric acid and 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 object of the study was serum and urine levels of uric acid as well as calcium, magnesium, phosphates, chloride, sodium, potassium, creatinine, urea and glucose. **Results**. Among all registered parameters, 12 were identified as characteristic of the four variants of uric acid metabolism. The discriminant model includes, in addition to uricosuria and uricemia by definition, blood levels of creatinine, urea, glucose, phosphates, magnesium, and potassium, creatinineuria as well as body mass index, electrokinetic index and sex 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 diuresis and excretion of urea, magnesium, sodium, phosphates, calcium, potassium and chloride, as well as calciumemia and magnesiumemia. **Conclusion**. The uric acid molecule, as a structural analog of methylxanthines and adenosine, exerts the metabolic effects, probably, as the consequences of its neuro-endocrine effects.
Keywords: uric acid, electrolytes, glucose, urea, creatinine, relationships.

INTRODUCTION

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 autonomic nervous, endocrine, and immune systems, the levels of which correlate with uricemia and/or uricosuria [3,4,10,11,21,23]. Similar tests were conducted in an experiment on healthy rats [1,2,7,8,9,20]. The **aim** of this study is to clarify the relationship between parameters of uric acid and other metabolites exchange, 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) [22].

Daily urine was collected, in which was determined the concentration of uric acid (estimated by uricase method), creatinine (by Jaffe's color reaction by Popper's method) and urea (urease method by reaction with phenolhypochlorite) as well as 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). Urine lithogenicity index (Lith) calculated by the Tiselius' HS [24] formula modifed by Flyunt VR et al [6]:

Lith = $(\text{Uric acid}\cdot\text{Calcium}/\text{Magnesium}\cdot\text{Creatinine})^{0,25}$.

The same metabolic parameters were determined in plasma as well as glucose (glucose-oxidase method). The analysis carried out according to instructions [6] with the use of flaming spectrophotometer "СФ-46", analyzers "Reflotron" (BRD) and "Pointe-180" (USA) and corresponding sets of reagents.

Given its integral physiological nature [12,15,16,17,18], we determined also the electrokinetic index (EKI) as rate of electronegative nuclei of buccal epithelium by intracellular microelectrophoresis on the device "Biotest" (produced by Karmazin National University, Kharkiv).

Normal (reference) values of variables are taken from the instructions and/or database of the Truskavetsian Scientific School of Balneology [6,13,22].

For statistical analysis used the software package "Microsoft Excell" and "Statistica 6.4 StatSoft Inc" (Tulsa, OK, USA).

RESULTS

Discriminant analysis was used to identify the specific metabolic accompaniment of clusters of uric acid exchange [14]. From among all the registered parameters, the forward stepwise program selected 12 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, plasma **electrolytes** magnesium, potassium and phosphates, **non-electrolytes** glucose, urea and creatinine and urine creatinine, as well as **integral** markers of metabolism such as body mass index and electrokinetic index and sex as a metabolotropic factor.

Table 1. Summary of discriminant function analysis for metabolic parameters exchange

Step 12, N of vars in model: 12; Grouping: 4 grps; Wilks' Λ: 0,0570; approx. $F_{(36)}$=9,8; $p<10^{-6}$

Variables currently in the model	Clusters of Uric Acid Exchange (n)				Parameters of Wilks' Statistics					
	S-E2+ IV (22)	**S± E+ I (21)**	**S2- E+ II (15)**	**S± E- III (30)**	Wilks Λ	Partial Λ	F-remove (3,7)	p-level	Tolerancy	Norm Cv (30)
Uricosuria, mM/24 h	5,94	3,94	3,88	2,27	0,289	0,197	98,9	10^{-6}	0,865	3,00 0,250
Uricemia,	0,316	0,371	0,249	0,322	0,079	0,723	9,31	10^{-4}	0,679	0,365

mM/L										0,116
Sex Index (M=1; F=2)	1,18	1,24	1,07	1,33	0,065	0,872	3,57	0,018	0,610	1,23 0,344
Magnesium Plasma, mM/L	0,826	0,856	0,831	0,822	0,067	0,849	4,32	0,007	0,812	0,90 0,056
Electrokinetic Index, %	48,3	43,6	42,7	40,4	0,063	0,906	2,52	0,064	0,684	40,9 0,250
Body Mass Index, kg/m^2	27,5	28,1	25,9	26,9	0,061	0,929	1,873	0,142	0,651	24,2 0,133
Glucose Plasma, mM/L	4,57	4,11	4,94	4,69	0,061	0,930	1,84	0,147	0,843	4,70 0,160
Phosphates Plasma, mM/L	0,96	0,97	1,09	1,06	0,061	0,937	1,64	0,188	0,884	1,20 0,167
Potassium Plasma, mM/L	4,40	4,40	4,50	4,19	0,063	0,906	2,53	0,064	0,762	4,55 0,104
Urea Plasma, mM/L	6,13	6,22	6,09	5,70	0,061	0,936	1,663	0,182	0,572	5,0 0,330
Creatininuria, mM/24 h	9,43	9,27	7,21	6,71	0,061	0,928	1,874	0,141	0,682	11,0 0,330
Creatinine Plasma, µM/L	85,6	87,4	88,1	84,0	0,061	0,940	1,56	0,207	0,396	77,5 0,172

Table 2. Summary of forward stepwise analysis of metabolic parameters

Variables currently in the model	F to enter	p-level	**Λ**	F-value	p-level
Uricosuria, mM/24 h	154	10^{-6}	0,154	154	10^{-6}
Uricemia, mM/L	8,47	10^{-4}	0,118	52,9	10^{-6}
Sex Index (M=1; F=2)	3,93	0,011	0,103	34,3	10^{-6}
Magnesium Plasma, mM/L	3,41	0,021	0,091	26,3	10^{-6}
Electrokinetic Index, %	1,62	0,191	0,086	21,1	10^{-6}
Body Mass Index, kg/m^2	1,51	0,219	0,082	17,7	10^{-6}
Glucose Plasma, mM/L	1,76	0,161	0,076	15,5	10^{-6}
Phosphates Plasma, mM/L	1,41	0,246	0,072	13,7	10^{-6}
Potassium Plasma, mM/L	1,56	0,205	0,068	12,4	10^{-6}
Urea Plasma, mM/L	1,27	0,291	0,065	11,3	10^{-6}
Creatininuria, mM/24 h	1,72	0,169	0,061	10,5	10^{-6}
Creatinine Plasma, µM/L	1,56	0,207	0,057	9,84	10^{-6}

Instead, urinary excretion of urea and all registered electrolytes, lithogenicity of urine, as well as age, despite their obvious recognition ability, were outside the discriminant model, apparently due to duplication/redundancy of information (Table 3).

Table 3. Parameters of metabolism, not included in the model

Variables	**Clusters of Uric Acid Exchange (n)**				**Parameters of Wilks' Statistics**						
	S-E2+ IV (22)	**S± E+ I (21)**	**S2- E+ II (15)**	**S± E- III (30)**	Wilks Λ	Partial Λ	F to enter	p-level	Tolerancy	Reference mean (30)	Cv
Urea Excretion, mM/24 h	796	566	548	407	0,055	0,967	0,81	0,491	0,520	458	0,186
Diurese, L/24 h	2,59	2,00	2,05	1,51	0,055	0,966	0,85	0,469	0,515	1,40	0,274
Calcium Excretion, mM/24 h	6,37	5,23	5,13	3,96	0,055	0,963	0,92	0,438	0,748	4,38	0,214
Magnesium Excretion, mM/24 h	5,74	5,13	4,31	3,68	0,056	0,977	0,56	0,641	0,718	4,10	0,266
Phosphates Excretion, mM/24 h	30,5	25,7	23,3	18,1	0,056	0,980	0,50	0,683	0,707	25,2	0,294

Chloride Excretion mM/24 h	277	214	208	156	0,056	0,988	0,30	0,834	0,766	167,5	0,172
Sodium Excretion, mM/24 h	262	211	218	179	0,056	0,978	0,55	0,652	0,738	154	0,211
Potassium Excretion, mM/24 h	87	71	65	66	0,055	0,971	0,70	0,552	0,484	65	0,269
(UA•Ca)/(Cr•Mg)^{0,25} Lithogenicity Urine	0,93	0,83	0,91	0,78	0,055	0,973	0,66	0,581	0,368	0,73	0,300
Age, Years	44,6	48,9	57,5	53,1	0,056	0,980	0,49	0,687	0,046	49,7	0,256
Calcium Plasma, mM/L	2,20	2,21	2,16	2,21	0,056	0,988	0,28	0,837	0,699	2,30	0,065
Chloride Plasma, mM/L	100	103	99,5	105	0,055	0,964	0,90	0,445	0,776	101,5	0,032
Sodium Plasma, mM/L	141	144	140	146	0,055	0,964	0,90	0,445	0,776	145	0,034

Following the algorithm [19,22], we transform the 12-dimensional space of discriminant variables into the 3-dimensional space of canonical roots. The canonical correlation coefficient for the first root is 0,928 (Wilks' Λ=0,057; $\chi^2_{(36)}$=226; p<10^{-6}), for the second 0,679 (Wilks' Λ=0,412; $\chi^2_{(22)}$=70; p=10^{-6}), for the third 0,487 (Wilks' Λ=0,763; $\chi^2_{(10)}$=21; p=0,019). The major root contains 84,2% of the discriminant possibilities, the second – 11,6%, and the minor - only 4,2%.

Calculating the values of the discriminant roots for each person based on raw coefficients and constants (Table 4) allows to visualize each patient in the information space of these roots.

Table 4. Standardized and raw coefficients and constants for metabolic parameters

Coefficients	**Standardized**			**Raw**		
Variables	Root 1	Root 2	Root 3	Root 1	Root 2	Root 3
Uricosuria, mM/24 h	-1,030	0,104	0,197	-1,710	0,172	0,327
Uricemia, mM/L	-0,094	-0,897	0,350	-1,304	-12,39	4,833
Sex Index (M=1; F=2)	-0,035	-0,535	0,569	-0,084	-1,281	1,360
Magnesium Plasma, mM/L	-0,089	-0,124	-0,852	-2,376	-3,326	-22,81
Electrokinetic Index, %	-0,314	-0,333	-0,075	-0,0267	-0,0282	-0,0064
Body Mass Index, kg/m^2	-0,070	-0,468	0,139	-0,020	-0,133	0,039
Glucose Plasma, mM/L	0,167	0,273	0,328	0,181	0,297	0,357
Phosphates Plasma, mM/L	-0,052	0,372	-0,150	-0,261	1,887	-0,760
Potassium Plasma, mM/L	0,035	0,353	-0,525	0,064	0,643	-0,958
Urea Plasma, mM/L	0,158	-0,421	-0,191	0,138	-0,367	-0,166
Creatininuria, mM/24 h	-0,016	-0,154	-0,629	-0,0045	-0,043	-0,177
Creatinine Plasma, µM/L	-0,069	0,397	-0,564	-0,005	0,030	-0,042
			Constants	9,602	6,431	23,08

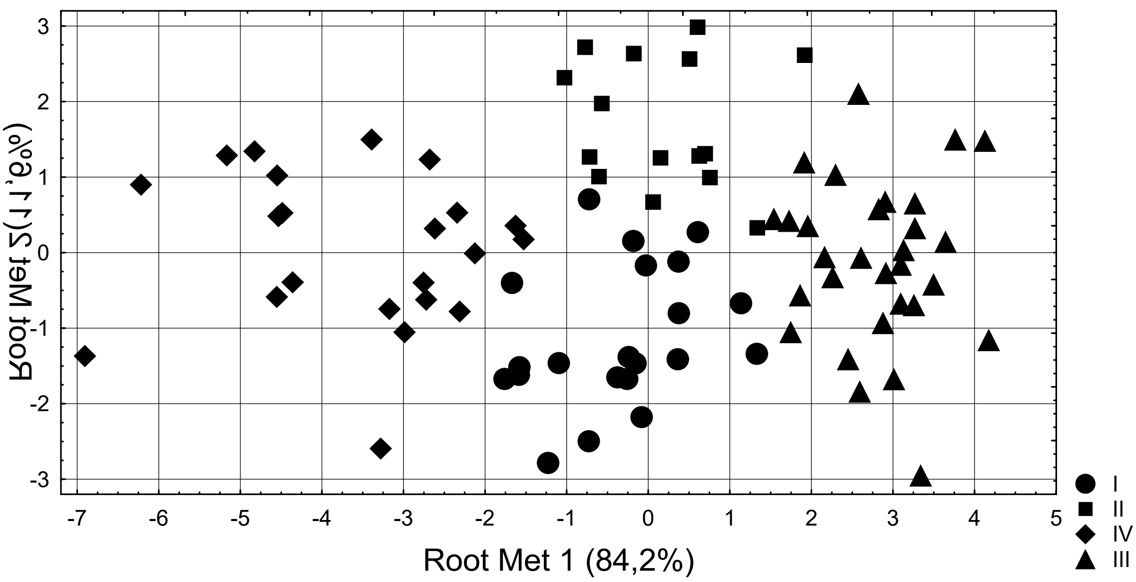
At the next stage of the analysis, the actual values of the parameters were normalized and grouped into three discriminant roots based on the structural coefficients (Table 5). In addition to discriminant variables, the table also presents variables that are not included in the model, but are still informal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

Table 5. Correlations of variables with canonical roots, root mean values and Z-values of metabolic parameters

Variables	**Correlations Variables-Roots**			**S-E2+ IV (22)**	**S±E+ I (21)**	**S2-E+ II (15)**	**S±E- III (30)**
Root 1 (84,2%)	**R 1**	**R 2**	**R 3**	**-3,60**	-0,36	+0,19	**+2,80**
Uricosuria	**-0,939**	0,140	0,037	**+3,87**	+1,26	+1,17	**-0,97**
Creatininuria	**-0,126**	-0,175	-0,131	-0,47	-0,52	-1,15	**-1,30**
Electrokinetic Index	**-0,118**	-0,031	0,056	**+0,73**	+0,26	+0,17	**-0,05**
Urea Plasma	**-0,061**	-0,017	-0,211	+0,69	+0,74	+0,66	**+0,42**

Potassium Plasma	**-0,059**	0,084	-0,253	-0,32	-0,31	-0,10	**-1,55**
Creatinine Plasma	**-0,019**	0,029	-0,195	+1,18	+1,33	+1,38	**+1,09**
Phosphates Excretion	currently not in model			**+0,71**	+0,06	-0,26	**-0,96**
Urea Excretion	currently not in model			**+3,96**	+1,27	+1,06	**-0,60**
Calcium Excretion	currently not in model			**+2,13**	+0,91	+0,81	**-0,44**
Magnesium Excretion	currently not in model			**+1,56**	+0,99	+0,20	**-0,40**
Chloride Excretion	currently not in model			**+3,82**	+1,61	+1,42	**-0,38**
Sodium Excretion	currently not in model			**+3,31**	+1,75	+1,97	**+0,76**
Potassium Excretion	currently not in model			**+1,25**	+0,36	+0,01	**+0,06**
Lithogenicity Urine	currently not in model			**+0,89**	+0,44	+0,79	**+0,23**
Diurese	currently not in model			**+3,11**	+1,56	+1,70	**+0,28**
Age	currently not in model			**-0,40**	-0,06	+0,14	**+0,27**
Root 2 (11,6%)	**R 1**	**R 2**	**R 3**	+0,05	**-1,13**	**+1,73**	-0,11
Uricemia	-0,012	**-0,587**	-0,049	-0,70	**+0,09**	**-1,89**	-0,53
Body Mass Index	-0,033	**-0,213**	-0,021	+1,02	**+1,21**	**+0,52**	+0,83
Magnesium Plasma	-0,029	**-0,206**	-0,553	-1,47	**-0,87**	**-1,36**	-1,35
Sex Index	0,055	**-0,161**	0,196	-0,11	**+0,02**	**-0,39**	+0,24
Sodium Plasma	currently not in model			-0,86	**-0,11**	**-1,01**	+0,27
Calcium Plasma	currently not in model			-0,69	**-0,60**	**-0,94**	-0,61
Chloride Plasma	currently not in model			-0,45	**+0,46**	**-0,63**	+0,92
Glucose Plasma	0,030	**0,303**	0,206	-0,17	**-0,78**	**+0,32**	-0,01
Phosphates Plasma	0,088	**0,213**	-0,004	-1,21	**-1,17**	**-0,53**	-0,69
Root 3 (4,2%)	**R 1**	**R 2**	**R 3**	+0,49	-0,69	-0,60	+0,42

As we can see in Fig. 1, members of the **S±E** cluster most clearly stand out from others, the characteristic features of which are a combination of hypouricosuria with hypokalemia and hypocreatininuria, while the level of creatinine in the plasma is elevated to the minimum extent for the sample, and the level of urea is at the upper limit and also minimal. Another characteristic feature is the normal, but minimal for the sample electrokinetic index. It is worth noting a number of parameters that were left out of the model, probably due to duplication and redundancy of recognition information. In particular, these are hypophosphaturia, lower limit levels of excretion of urea, calcium, magnesium and chloride, normal, but minimal for the sample, levels of natriuria, kaliuria and diuresis, as well as lithogenicity of urine. Instead, the members of this cluster were on average the oldest in the sample.



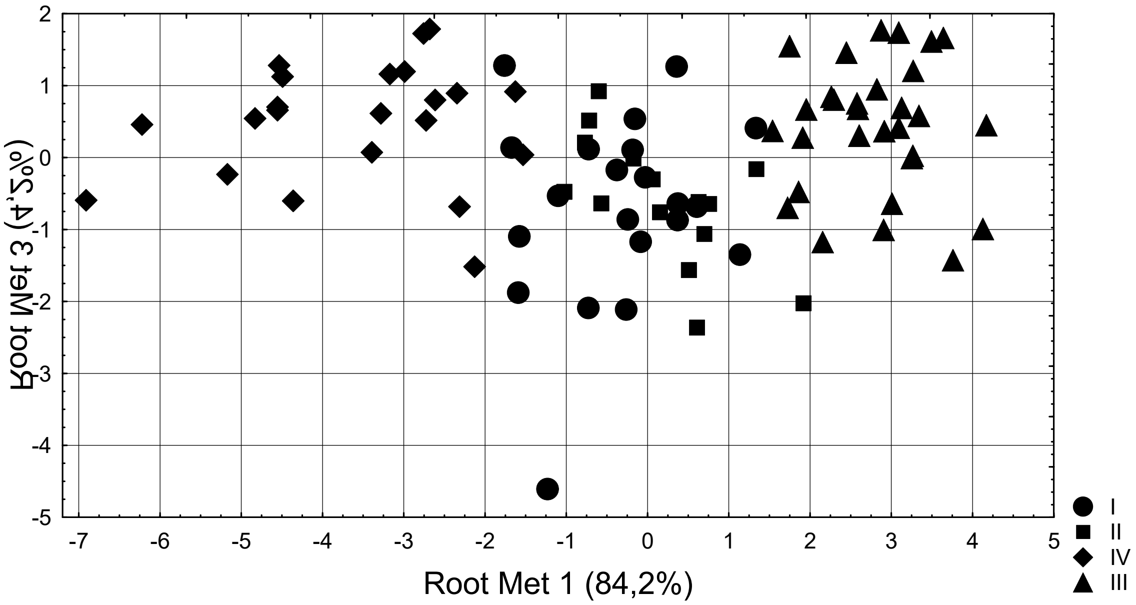


Fig. 1. Scattering of individual values of the first and second (top) and first and third (bottom) discriminant metabolic roots of patients from different clusters

At the other pole of the axis of the first root are members of the S-E2+ cluster, in which hyperuricosuria is accompanied by higher levels of the already mentioned parameters, as well as maximally increased electrokinetic index, diuresis, excretion of urea, chloride, calcium, magnesium, sodium and potassium, and lithogenicity of urine. In addition, the members of this cluster were on average the youngest in the sample.

Members of the other two clusters occupy an intermediate position along the axis of the first root and are mutually mixed. Instead, they are quite clearly demarcated along the axis of the second root. The top position of patients of the **S2-E+** cluster reflects the combination of hypouricemia with hypomagnesemia and, maximally for the sample, reduced levels in plasma of sodium, calcium, and chloride and a normal body mass index, instead, maximally for the sample, normal glycemia and low-limit phosphateemia. At the same time, there is only one woman among the 15 members of the cluster. In the members of the **S±E+** cluster located below, the listed parameters are significantly **higher**/**lower**, and among 16 people, there are 5 women.

The third discriminant root carries no additional information. So that all four clusters are quite clearly demarcated by the set of discriminant variables in the information space of even two roots (Table 6).

Table 6. Mahalanobis distances between clusters, F-criterions (df=12,7) and p-levels

Clusters	**S±E+ I**	**S2-E+ II**	**S-E2+ IV**	**S±E- III**
S±E+ I (21)	0	8,4	13,3	12,2
S2-E+ II (15)	**5,3** 10^{-5}	0	18,3	11,2
S-E2+ IV (22)	**10,3** 10^{-6}	**11,8** 10^{-6}	0	40,9
S±E- III (30)	**10,9** 10^{-6}	**8,1** 10^{-6}	**37,6** 10^{-6}	0

With the help of classification functions (Table 7), we will find out the possibility of identifying the belonging of this or that person to this or that cluster.

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	9,453	9,042	15,58	4,600
Uricemia, mM/L	47,74	12,13	43,09	36,42
Sex Index (M=1; F=2)	-4,855	-8,430	-4,484	-4,908
Magnesium Plasma, mM/L	808,0	795,1	784,8	771,7
Electrokinetic Index, %	1,438	1,342	1,484	1,318
Body Mass Index, kg/m²	2,996	2,610	2,950	2,843
Glucose Plasma, mM/L	0,426	1,405	0,610	1,697
Phosphates Plasma, mM/L	62,97	68,15	65,15	63,22
Potassium Plasma, mM/L	19,24	21,03	18,66	19,04
Urea Plasma, mM/L	5,491	4,503	4,415	5,368
Creatininuria, mM/24 h	2,460	2,317	2,214	2,204
Creatinine Plasma, μM/L	0,892	0,970	0,894	0,859
Constants	-586,8	-562,2	-588,6	-527,0

As you can see, in retrospect, it is possible to recognize members of the most numerous cluster III without error, and others - with 1-2 errors, so that the classification accuracy is 94.3% (Table 8).

Table 8. Classification matrix for clusters

Rows: observed classifications; columns: predicted classifications

Clusters	Percent correct	S±E+ I p=,239	S2-E+ II p=,170	S-E2+ IV p=,250	S±E- III p=,341
I	90,5	**19**	1	0	1
II	93,3	0	**14**	0	1
IV	90,9	2	0	**20**	0
III	100	0	0	0	**30**
Total	94,3	21	15	20	32

Now let's consider correlations between parameters of uric acid metabolism, on the one hand, and electrolytes, non-electrolytes, and metabolic markers - on the other hand (Table 9).

Table 9. Correlation matrix for uric acid and other metabolites parameters

	Uricemia raw	Uricemia normalized	Uricosuria
Sex Index	-0,29	0,20	-0,15
Age	0,02	-0,03	-0,19
Electrokinetic Index	-0,09	-0,02	0,22
Body Mass Index	0,13	0,09	0,10
Creatinine Plasma	0,23	0,02	0,07
Urea Plasma	0,02	-0,10	0,22
Glucose Plasma	-0,35	-0,28	-0,01
Calcium Plasma	0,28	0,22	-0,03
Phosphates Plasma	-0,04	-0,06	-0,23
Magnesium Plasma	0,11	0,23	0,04
Potassium Plasma	-0,04	0,08	0,16
Chloride Plasma	0,32	0,38	-0,28
Sodium Plasma	0,32	0,38	-0,28
Diuresis	0,12	0,01	0,65
Creatininuria	-0,04	0,10	0,30
Urea Excretion	0,12	0,02	0,71
Calcium Excretion	0,12	0,03	0,38
Phosphates Excretion	0,18	0,10	0,37

Magnesium Excretion	0,16	0,14	0,44
Potassium Excretion	0,14	0,08	0,27
Chloride Excretion	-0,06	-0,07	0,51
Sodium Excretion	0,04	0,00	0,36
Lithogenicity Urine	-0,04	-0,23	0,42

It was found that uricosuria has more numerous and closer correlations with metabolic parameters than uricemia.

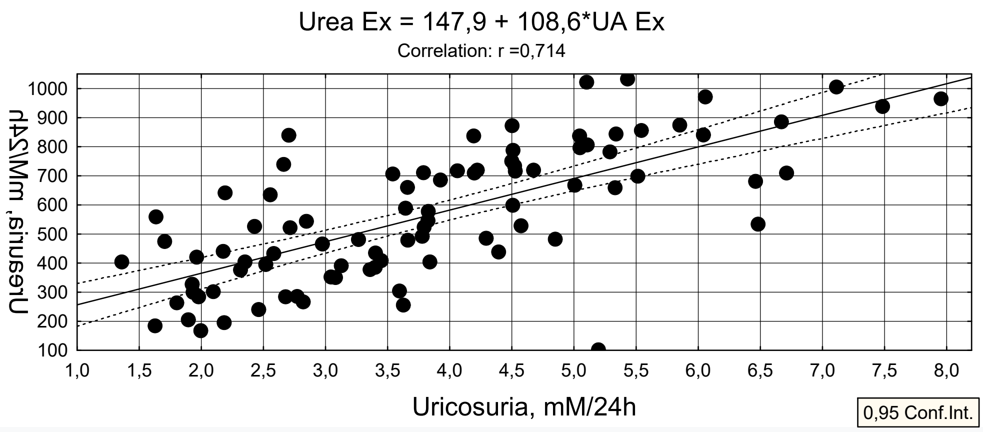


Fig. 2. Scatterplot of the correlation between uricosuria (line X) and ureauria (line Y)

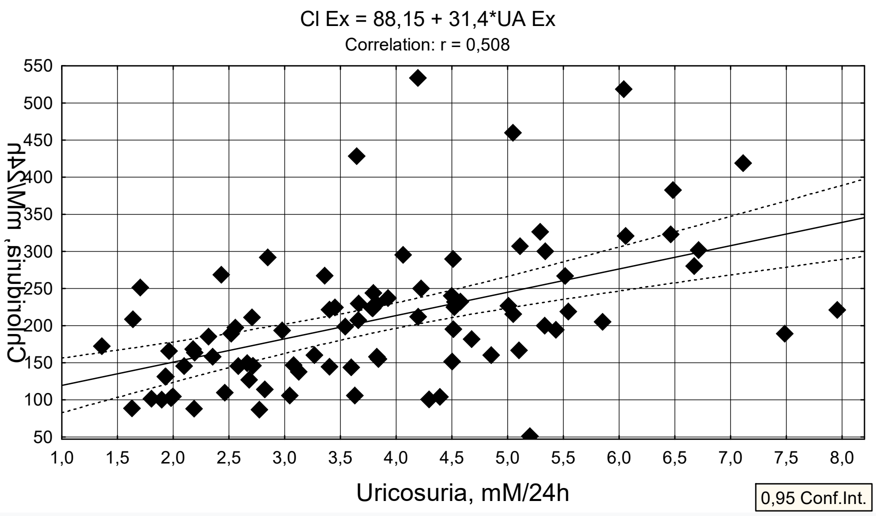


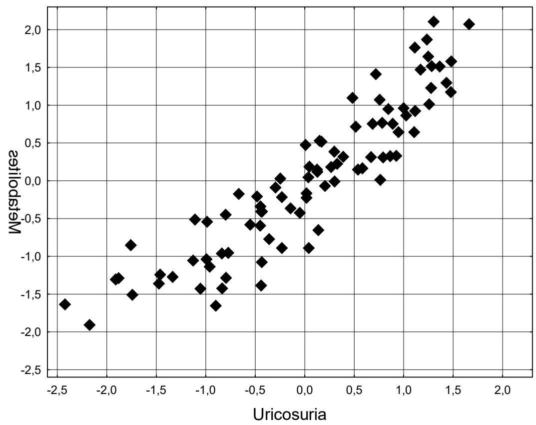
Fig. 3. Scatterplot of the correlation between uricosuria (line X) and chloriduria (line Y)

First of all, this concerns the excretion of urea (Fig. 2) and chloride (Fig. 3).

In the regression model, after stepwise exclusion, in addition to these parameters, chloridemia and kaliemia, excretion of creatinine, calcium and magnesium, as well as caused by them the lithogenicity of urine, were found. This metabolic constellation is determined by uricosuria by 81% (Table 10 and Fig. 4).

Table 10. Regression model for metabolic parameters and uricosuria

N=88	R=0,911 ; R^2=0,830; Adjusted R^2=0,813; F(8,8)=48; p<10^-6 Beta	St. Err. of Beta	B	St. Err. of B	t(79)	p-value
Intercpt			-5,387	1,509	-3,57	0,000612
Creatinine E	0,475	0,068	0,193	0,028	6,94	0,000000
Ca E	-0,594	0,091	-0,290	0,044	-6,56	0,000000
Mg E	0,371	0,095	0,286	0,073	3,91	0,000197
Cl E	0,159	0,065	0,003	0,001	2,45	0,016523
Lithogenicity	0,798	0,078	7,856	0,772	10,17	0,000000
Cl P lasma	-0,083	0,049	-0,018	0,011	-1,70	0,093951
Urea E	0,412	0,073	0,003	0,000	5,61	0,000000
K Plasma	0,076	0,049	0,209	0,134	1,57	0,121253



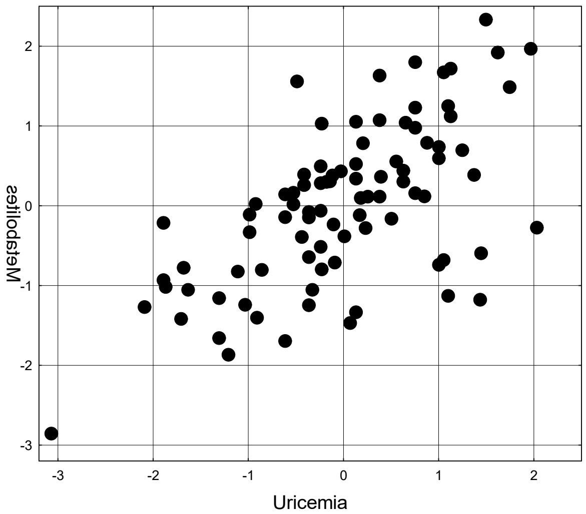
R=0,911; R^2=0,830; $\chi^2_{(8)}$=146; p<10^{-6}; Lambda Prime=0,170

Fig. 4. Scatterplot of the canonical correlation between uricosuria (line X) and other metabolic parameters (line Y)

It is interesting that magnesiumuria was included in the regression model for uricemia, and other components of the model were glycemia, chlorideemia, calciumemia, and creatinineemia. This metabolic constellation is determined by uricemia by 36% (Table 11 and Fig. 5).

Table 11. Regression model for metabolic parameters and raw uricemia

N=88	R=0,630; R^2=0,397; Adjusted R^2=0,360; F(5,8)=10,8; p<10^-5 Beta	St. Err. of Beta	B	St. Err. of B	t(82)	p-value
Intercpt			-0,5184	0,1736	-2,99	0,00372
Glucose	-0,278	0,089	-0,0238	0,0076	-3,13	0,00240
Ca P	0,315	0,091	0,1432	0,0413	3,46	0,00085
Cl P	0,393	0,089	0,0046	0,0010	4,42	0,00003
Cr P	0,247	0,086	0,0015	0,0005	2,86	0,00535
Mg E	0,163	0,086	0,0067	0,0036	1,89	0,06216



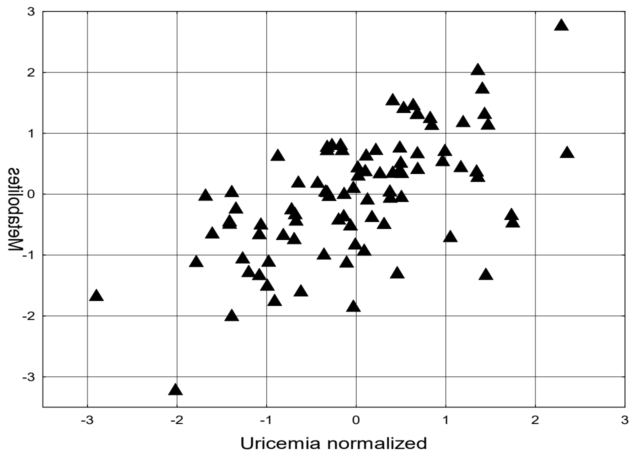
R=0,630; R^2=0,397; $\chi^2_{(5)}$=42; p<10^{-6}; Lambda Prime=0,603

Fig. 5. Scatterplot of canonical correlation between Uricemia (X-line) and other metabolic parameters (Y-line)

The same 4 parameters appeared in the regression model for uricemia, normalized by sex and age, together with magnesiumemia and urinary lithogenicity, but without creatinineemia. Such a metabolic constellation is determined by normalized uricemia by 33,5% (Table 12 and Fig. 6).

Table 12. Regression model for metabolic parameters and normalized uricemia

	R=0,617; R^2=0,381; Adjusted R^2=0,335; F(6,8)=8,3; p<10^-6					
N=88	Beta	St. Err. of Beta	B	St. Err. of B	t(81)	p-value
Intercpt			-14,162	3,343	-4,24	0,00006
Glucose	-0,213	0,091	-0,252	0,108	-2,34	0,02184
Ca P	0,305	0,093	1,911	0,582	3,28	0,00152
Cl P	0,358	0,095	0,058	0,015	3,76	0,00032
Mg E	0,180	0,089	0,103	0,051	2,02	0,04625
Lithogenicity	-0,173	0,093	-1,263	0,677	-1,87	0,06574
Mg P	0,216	0,090	6,153	2,571	2,39	0,01902



R=0,617; R^2=0,381; $\chi^2_{(6)}$=40; p<10^{-6}; Lambda Prime=0,619

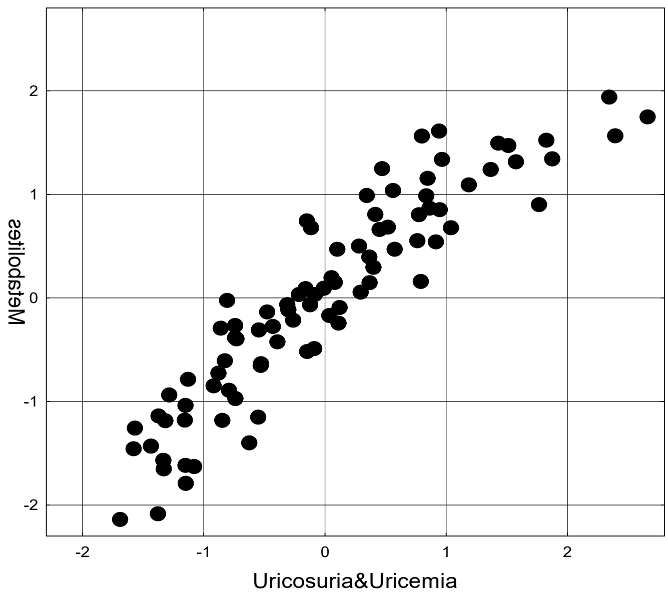
Fig. 6. Scatterplot of canonical correlation between normalized Uricemia (X-line) and other metabolic parameters (Y-line)

According to the results of the canonical correlation analysis, two pairs of canonical roots were formed. The uric acid root of the first pair mainly represents uricosuria. The metabolic canonical root receives the maximum positive factor load from ureauria, then there is a constellation of parameters with smaller, approximately equal burdens - chlorideuria, magnesiria, calciuria, creatinineuria and the associated lithogenicity of urine, and the minimum load on the root is given by potassiumemia. Instead, chloridemia gives a negative load on the metabolic root (Table 13). Uricose determination of this metabolic constellation is 85% (Fig. 7).

Table 13. Factor structure of the canonical roots of parameters of uric acid and other metabolites exchange

Variable	left set	
	Root 1	Root
Uricosuria	0,995	0,038
Uricemia raw	-0,083	0,987
Uricemia norm	-0,176	0,783

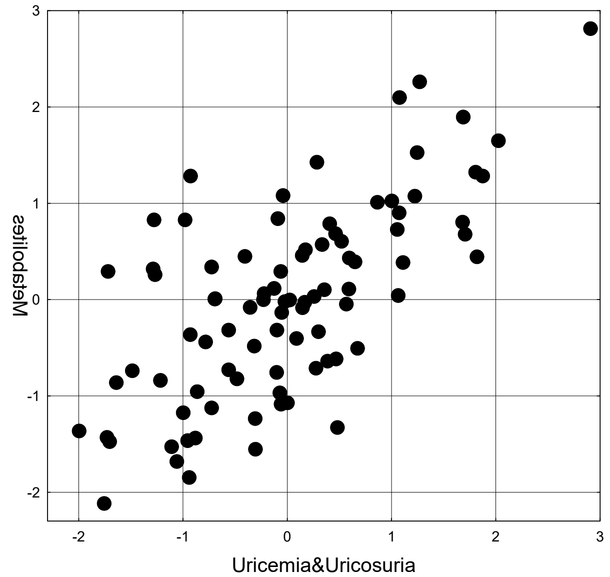
Variable	right set	
	Root 1	Root 2
Glucose	0,007	-0,514
Urea Excr	0,772	0,261
Ca P	-0,045	0,428
Mg P	0,015	0,099
K P	0,145	-0,108
Cl P	-0,335	0,408
Creatinine P	0,096	0,424
Ca Excr	0,412	0,247
Mg Excr	0,455	0,274
Cl Excr	0,548	-0,040
Lithogenicity	0,493	0,067
Creatininuria	0,301	-0,097



R=0,920; R^2=0,847; $\chi^2_{(36)}$=227; p<10^{-6}; Lambda Prime=0,056

Fig. 7. Scatterplot of canonical correlation between parameters of Uric acid exchange (X-line) and other metabolic parameters exchange (Y-line). First pair of Roots

The uric acid root of the second pair mainly represents uricemia. The metabolic canonical root receives the maximum inverse factor load from glycemia, smaller unidirectional loads with uricemia - from calciumemia, creatinineemia, and chloridemia, and minimum - from the excretion of magnesium, urea, and calcium. This metabolic constellation is determined by uric acid by 46% (Fig. 8).



R=0,675; R^2=0,456; $\chi^2_{(22)}$=79; p<10^{-6}; Lambda Prime=0,369

Fig. 8. Scatterplot of canonical correlation between parameters of Uric acid exchange (X-line) and other metabolic parameters exchange (Y-line). Second pair of Roots

It is time to move on to considering the relationship between the changes in the parameters of uric acid metabolism and other metabolites caused by the course of adaptogenic balneotherapy. The screening result is shown in the table. 14.

As we can see, the dynamics of uricosuria is closely related to the dynamics of daily diuresis and excretion of urea and creatinine. Magnesiuria, calciuria, phosphaturia and chlorideuria, as well as the lithogenicity of urine caused by them, are the second constellation of parameters with the strongest connections. Instead, changes in natriuria and kaliuria correlate with changes in uricosuria very weakly, as do changes in plasma levels of creatinine, urea, and potassium.

Table 14. Correlation matrix for changes in uric acid and other metabolites parameters

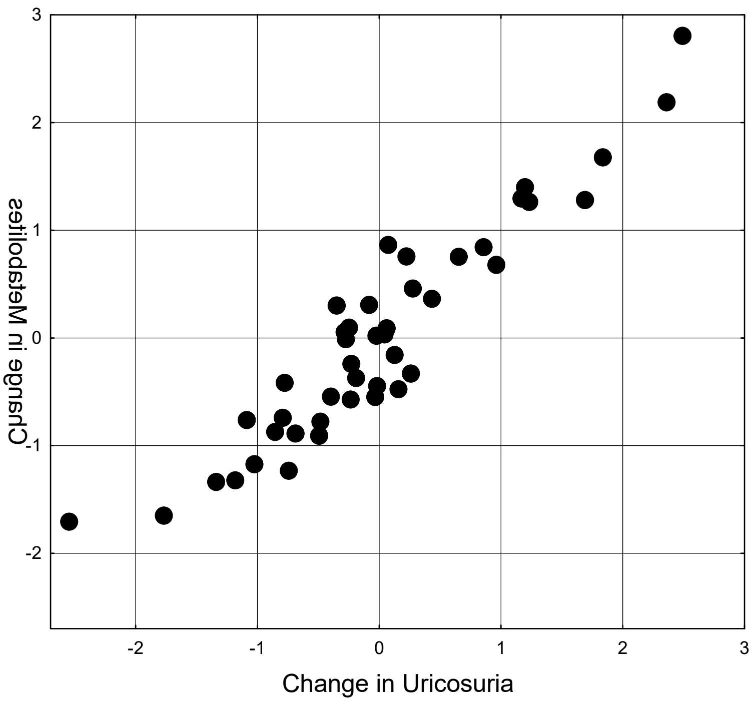
Variable	Uricemia	Uricosuria
Cr P	0,23	-0,25
Diurese	-0,03	0,79
Cr E	-0,02	0,60
Ca E	-0,20	0,36
Pi E	-0,15	0,34
Mg E	-0,04	0,38
K E	0,03	0,20
Cl E	0,12	0,32
Na E	0,14	0,15
Lithogenicity	-0,19	0,31
Ca P	0,28	0,06
Mg P	0,18	0,03
K P	-0,09	0,18
Cl P	0,26	-0,10
Na P	0,26	-0,10
Urea E	-0,06	0,77
Urea P	0,07	0,20

However, after step-by-step exclusion, the dynamics of kaliemia remained in the regression model, while the dynamics of chloriduria was left out of the model (Table 15).

Table 15. Regression model for changes in metabolic parameters and uricosuria

N=44	R=0,940; R^2=0,884; Adjusted R^2=0,853; F(9,3)=28; p<10^-5					
	Beta	St. Err. of Beta	B	St. Err. of B	t(34)	p-value
Intercpt			-0,5510	0,1268	-4,35	0,000119
Diurese	0,228	0,114	0,6896	0,3448	2,00	0,053533
Cr E	0,358	0,090	0,1553	0,0392	3,97	0,000356
Ca E	-0,593	0,128	-0,2604	0,0563	-4,62	0,000053
Pi E	0,186	0,082	0,0185	0,0082	2,26	0,030115
Mg E	0,245	0,100	0,2089	0,0853	2,45	0,019580
K E	0,178	0,103	0,0064	0,0037	1,73	0,092282
Lithogenicity	0,625	0,096	6,4268	0,9898	6,49	0,000000
K P	0,227	0,109	0,6315	0,3044	2,07	0,045666
Urea E	0,350	0,108	0,0030	0,0009	3,25	0,002624

The dynamics of this constellation of metabolic parameters is determined by the dynamics of uricosuria by 88% (Fig. 9).



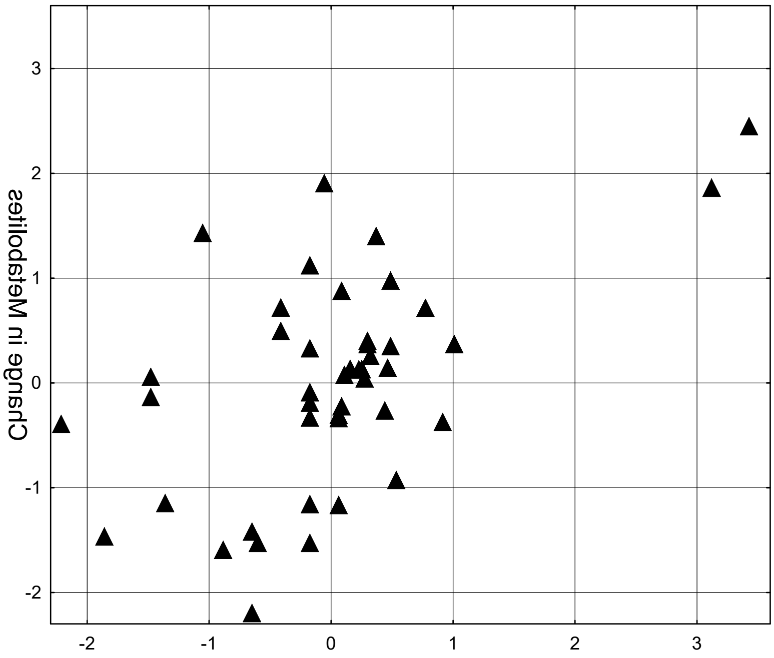
R=0,940; R^2=0,884; $\chi^2_{(9)}$=81; p<10^{-6}; Lambda Prime=0,116

Fig. 9. Scatterplot of canonical correlation between changes in Uricosuria (X-line) and other metabolic parameters (Y-line)

Instead, the dynamics of uricemia is related to the dynamics of metabolic parameters much weaker. It is surprising that in the process of step-by-step exclusion, the program left chlorideuria, natriuria, lithogenicity, and magnesiumemia in the regression model, while natriemia and creatinineemia were left out of the model. Obviously, this circumstance explains the significant difference (11,4%) between the actual and adjusted coefficients of determination (Table 16 and Fig. 10).

Table 16. Regression model for changes in metabolic parameters and uricemia

	R=0,544; R^2=0,295; Adjusted R^2=0,181; F(6,4)=2,6; p=0,034					
N=44	Beta	St. Err. of Beta	B	St. Err. of B	t(37)	p-value
Intercpt			-0,00365	0,00705	-0,52	0,608
Cl E	0,250	0,179	0,00009	0,00007	1,40	0,171
Na E	-0,345	0,213	-0,00015	0,00009	-1,62	0,114
Lithogenicity	-0,325	0,157	-0,08307	0,04025	-2,06	0,046
Ca P	0,453	0,152	0,10625	0,03556	2,99	0,005
Mg P	0,199	0,155	0,17439	0,13606	1,28	0,208
Cl P	0,349	0,154	0,00145	0,00064	2,27	0,029



$R=0{,}543$; $R^2=0{,}295$; $\chi^2_{(6)}=13{,}7$; $p=0{,}034$; Lambda Prime=0,705

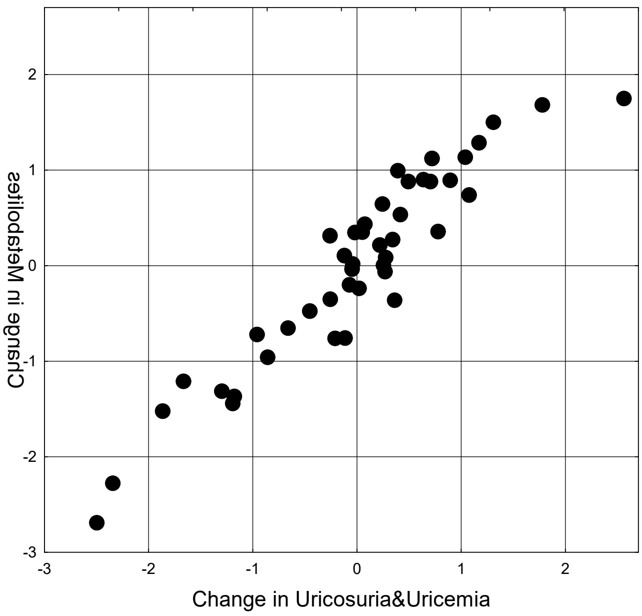
Fig. 10. Scatterplot of canonical correlation between changes in Uricemia (X-line) and other metabolic parameters (Y-line)

It is natural that according to the results of the canonical correlation analysis, the combined determination of the dynamics of metabolic parameters from the side of uricosuria and uricemia exceeds the effect of uricosuria itself by only 10% (Table 17 and Fig. 11).

Table 17. Factor structure of the canonical roots of changes in parameters of uric acid and other metabolites exchange

Root Variable	left set R
Uricemia	-0,058
Uricosuria	0,999

Root Variable	right set R
Cl E	0,333
Na E	0,185
Lithogenicity	0,341
Ca P	0,055
Mg P	0,020
Cl P	-0,115
Diurese	0,834
Cr E	0,637
Ca E	0,386
Pi E	0,371
Mg E	0,405
K E	0,207
K P	0,197
Urea E	0,813



R=0,946; R^2=0,894; $\chi^2_{(28)}$=93; p<10^{-6}; Lambda Prime=0,068

Fig. 11. Scatterplot of canonical correlation between changes in Uricosuria&Uricemia (X-line) and other metabolic parameters (Y-line)

CONCLUSION

Therefore, the exchange of uric acid is closely related to the exchange of other metabolites, at least electrolytes and nitrogenous compounds. A detailed analysis of the mechanisms of such connections will be carried out in the next article. Spoiler. Mediators are neuro-endocrine effects 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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