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PECULIARITIES OF METABOLIC AND AUTONOMIC-ENDOCRINE ACCOMPANIMENTS OF URATE-LOSING/RETAINING KIDNEYS

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Abstract

Background. This publication initiates the project "Neuro-endocrine regulation of the clearance of nitrogenous metabolites". The first stage of project implementation is the clarification of peculiarities of metabolic and neuro-endocrine accompaniments of urate-losing and urate-retaining kidneys. **Materials and Methods**. The object of observations were patients with chronic pyelonephritis in the phase of remission (34 males aged 23-70 years and 10 females aged 33-76 years). Testing was performed twice - on admission and after 7-10 days of standard balneotherapy on Truskavets Spa. The battery of tests was created in line with concepts functional-metabolic continuum and NEI network. The content of nitrogenous metabolites and electrolytes was determined in daily urine and blood serum. In addition, indicators of the lipoprotein spectrum and lipids peroxidation, as well as the level of the main adaptation hormones, were determined in the blood. The state of the autonomic nervous system was assessed by the HRV method. **Results**. In 63.6% of cases, the renal clearance of uric acid was within the classical norm (±2σ), in 12.5% it was moderately reduced, but in the remaining cases it was increased, including drastically in 3 cases. The method of discriminant analysis revealed 20 parameters, according to the totality of which all 4 clusters of uric acid clearance clearly differ from each other (classification accuracy 100%). **Conclusion**. Constitutionally distinct types of uric acid metabolism (euricosis, urate-losing and urate-retaining kidneys) are characterized by specific constellations of metabolic and autonomic-endocrine parameters.

Keywords: uric acid clearance, urine and serum metabolites and electrolytes, lipids peroxidation, HRV, adaptation hormones, chronic pyelonephritis.

INRODUCTION

A 100-year history of basic and clinical studies supports UA being a direct risk factor for chronic kidney disease (CKD). Nevertheless, controversy exists over the causal role of UA in the development or exacerbation of CKD, with conflicting results being produced in various studies. Although many nephrologists currently treat asymptomatic patients with hyperuricemia, there is no consensus on the appropriateness of such a treatment approach. Furthermore, hypouricemia has been shown to increase the risk for deterioration of renal function, making it more difficult to set a target range for the optimal serum UA level. In the CARES trial, all-cause and cardiovascular mortality were higher in the febuxostat group than in the allopurinol group, even though patients receiving febuxostat had lower serum UA levels. The higher mortality associated with this more intense UA-lowering therapy is consistent with the U-shaped association between UA and mortality proposed in some observational studies. Because UA is the most abundant antioxidant in plasma, strategies to increase UA are ongoing in clinical trials of patients with neurological diseases. Further research is needed to assess the safety of lowering serum UA to specific thresholds to produce safe guidelines. Optimal serum UA levels should be defined at both upper and lower limits, for men and women, and in patients with and without CVD or CKD. Although hyperuricemia has been associated with CKD in many studies, it remains controversial whether this is the cause or the result of decreased renal function. Recent observational studies of healthy populations and patients with CKD have reported that UA has an independent role in the development or progression of CKD. Experimental studies have shown several potential mechanisms by which hyperuricemia may cause or promote CKD. However, other reports have indicated an association between hypouricemia and CKD. This opposing effect is hypothesized to occur because UA is a major antioxidant in human plasma and is associated with oxidative stress [29]. Elevated serum urate concentration is the primary cause of gout. Understanding the processes that affect serum urate concentration is important for understanding the etiology of gout and thereby understanding treatment [19].

Back in 1989, Karve MD et al [21] put forward the concept of the "urate-retaining" and "urate-losing" kidney as a reflection of constitutionally different types of uric acid metabolism, due to the heterogeneity of filtration-reabsorption mechanisms and endocrine functions of the kidneys, which leads to hyperuricemia in some individuals or hypouricemia in others. However, judging by the lack of subsequent publications on the subject, the concept has been largely ignored by the scientific community. Only in 2004, this concept attracted the attention of Ivassivka SV et al [20]. Among 200 patients of the Truskavets' spa, the authors found uric acid clearance in the range of 50÷150% of the average norm in 79, while 103 were diagnosed with "urate-losing" kidneys and only 18 with "urate-retaining" kidneys. However, the case did not go beyond the establishment of different types of uric acid exchange.

Given the known wide spectrum of physiological activity of uric acid [4,6,10,24,27], we set ourselves the goal of identifying peculiarities of metabolic and neuro-endocrine accompaniments of urate-losing and urate-retaining kidneys.

MATERIALS AND METHODS

The object of observations were patients with chronic pyelonephritis in the phase of remission (34 males aged 23-70 years and 10 females aged 33-76 years). 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) [28,30].

The battery of tests was created in line with concepts functional-metabolic continuum [12,18] and NEI network [15,31]. It is known about the existence of close functional link between adequate working kidney nephrons and bone metabolism. Focused monitoring of renal function is able to provide 482 substantial assistance in the organization of preventive measures against latently emerging osteoporosis [13]. Activation of lipids peroxidation is known to inhibit glomerular filtration, whereas antioxidants prevent this [7,14,16,34]. These facts became the basis for determining calcitonin, PTH and parameters of lipids peroxidation. The known connections of urinary uric acid with the parameters of the autonomic nervous and endocrine systems [4,24] became the basis for determining the parameters of HRV and adaptation hormones.

Daily urine was collected on the eve, 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 lytogenicity index calculated by the Tiselius' HS [33] formula modifed by Flyunt VR et al [8]: Lytogenicity = $(UA \bullet Ca/Mg \bullet Creatinine)^{0,25}$.

The same metabolic parameters were determined in serum as well as total cholesterol and content of it in composition of HD, LD and VLD lipoproteins) [11]; diene conjugates (spectrophotometry of heptane phase of lipids extract) [9]) and malondialdehyde (test with tiobarbiture acid) [2], as well as the activity of antioxidant enzymes: catalase serum (by the speed of decomposition hydrogen peroxide) [25] and superoxide dismutase erythrocytes (by the degree of inhibition of nitroblue tetrazolium recovery in the presence of N-methylphenazone metasulfate and NADH) [5,26]. The analysis carried out according to instructions [11] with the use of flaming spectrophotometer "СФ-46", analyzers "Reflotron" (BRD) and "Pointe-180" (USA) and corresponding sets of reagents.

In addition, we determined serum levels of main adaptation hormones such as Cortisol, Aldosterone, Testosterone, Triiodothyronine as well as Calcitonin and PTH (by the ELISA with the use of analyzer "RT-2100C" and corresponding sets of reagents from "Алкор Био", XEMA Co, Ltd and DRG International Inc). Systolic (Ps) and diastolic (Pd) blood pressure was measured (tonometer "Omron M4-I", Netherlands) in a sitting position three times in a row followed by the calculation of Ps2/Ps1, Ps3/Ps1, Pd2/Pd1, and Pd3/Pd2 rations [32]. The good old Stange's and Genchi's tests were carried out on occasion [3].

To assess the parameters of heart rate variability (HRV), recorded electrocardiogram during 7 min in II lead (hardware-software complex "CardioLab+HRV" produced by "KhAI-Medica", Kharkiv, Ukraine). For further analysis the following parameters HRV were selected. Temporal parameters (Time Domain Methods): heart rate (HR), the standard 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 ms (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). We calculated classical indexes: LF/HF, LFnu=100%•LF/(LF+HF), Centralization Index (VLF+LF)/HF [15,24,31].

Normal (reference) values of variables are taken from the instructions and/or database of our group [11,22,31]. For statistical analysis used the software package "Microsoft Excell" and "Statistica 6.4 StatSoft Inc" (Tulsa, OK, USA).

RESULTS

First of all, a complete lack of correlation was found between both components of clearance - uricosuria and uricemia (Fig. 1). That is, they are related to clearance independently (Fig. 2).

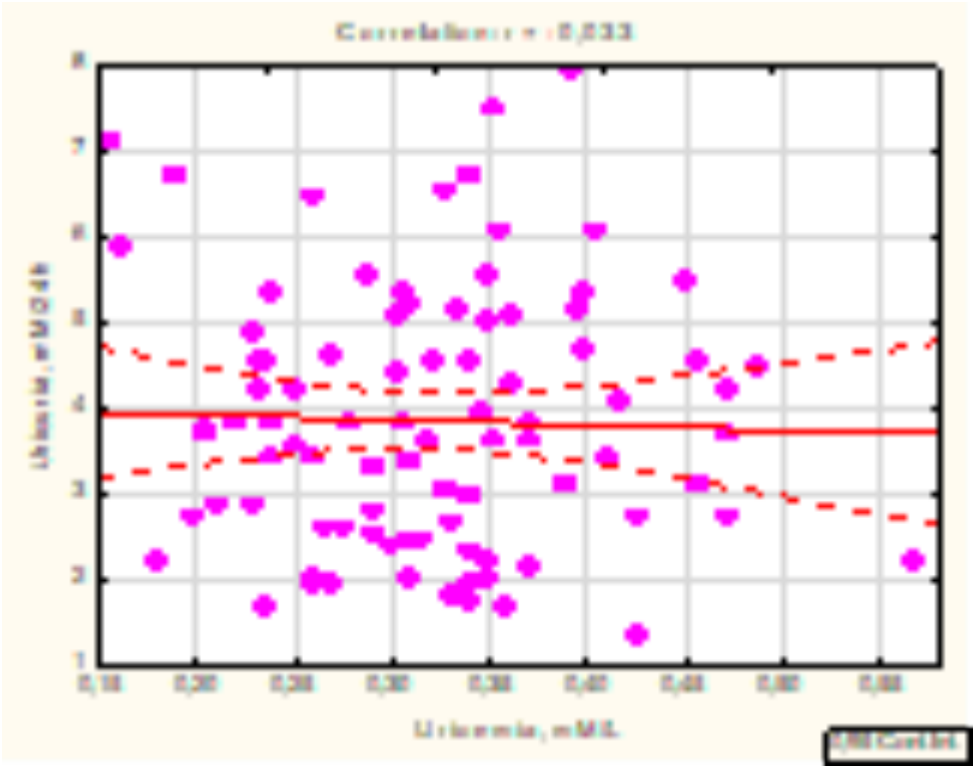


Fig. 1. Absence of correlation between uricemia and uricosuria

$Z(\pm 1{,}72) = 9{,}43(\pm 0{,}90) - 30{,}75(\pm 2{,}22)\bullet X + 2{,}45(\pm 0{,}12)\bullet Y$

$R=0{,}936$; $R^2=0{,}877$; Adj $R^2=0{,}874$; $F_{(2,9)}=302$; $p<10^{-6}$

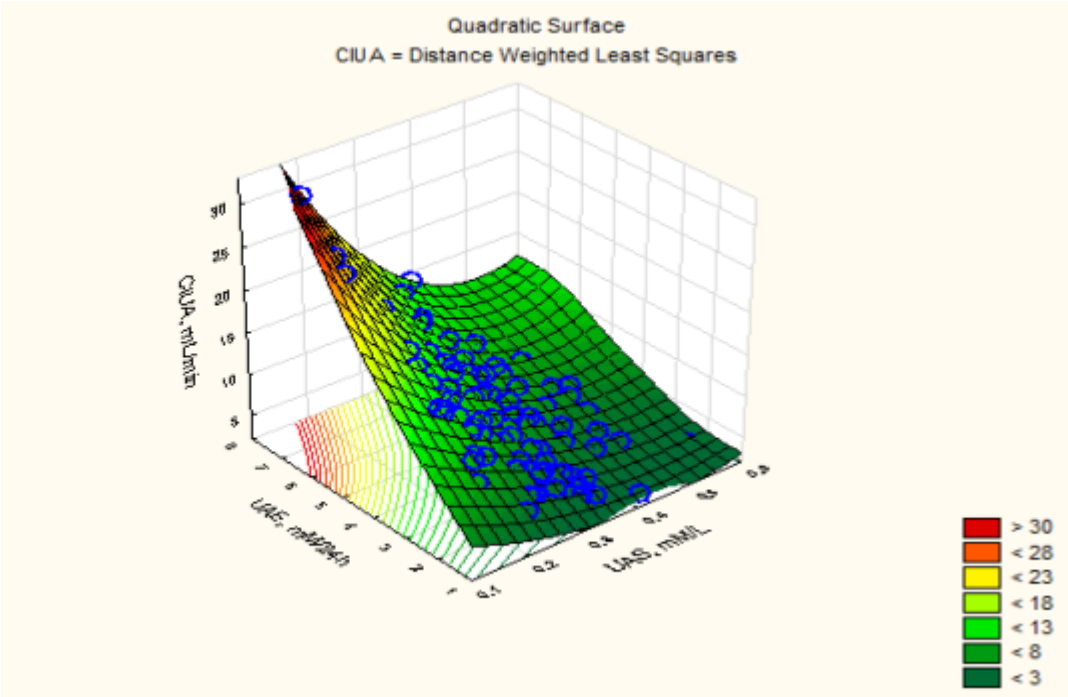


Fig. 2. Quadratic surface of relationship between uricemia (X-line), uricosuria (Y-line) and uric acid clearance (Z-line)

At the same time, uricosuria determines the clearance of uric acid by 61% (Fig. 3), and uricemia by only 37% (Fig. 4).

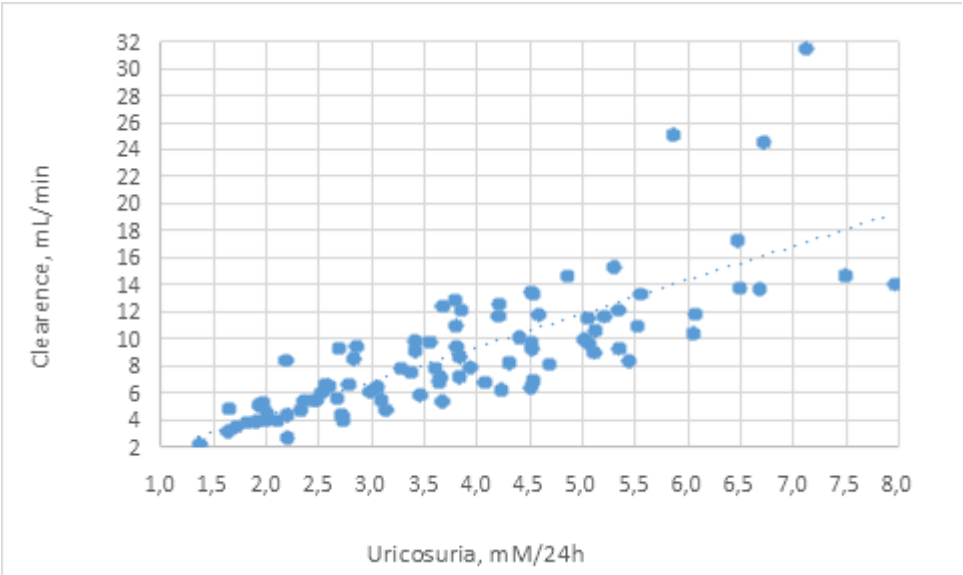


Fig. 3. Scatterplot of correlation between uricosuria (X-line) and uric acid clearance (Y-line)

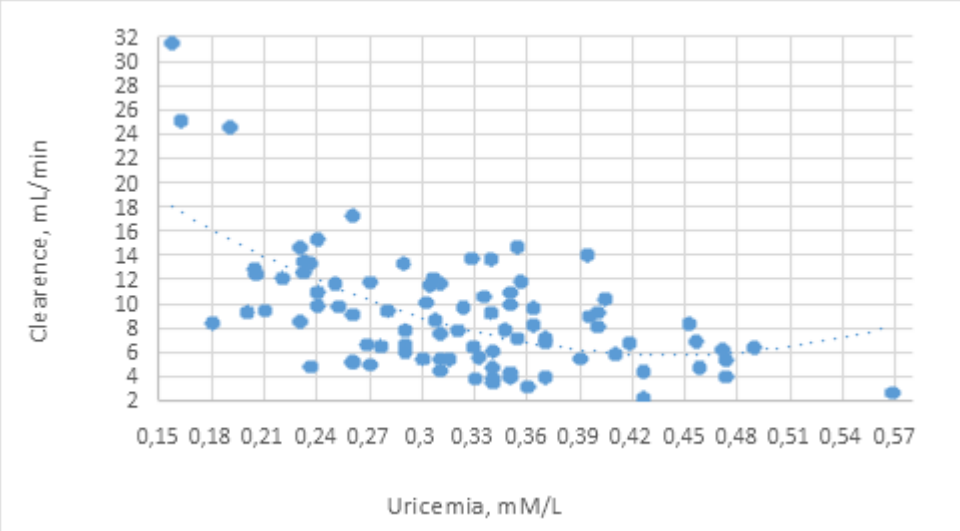


Fig. 4. Scatterplot of correlation between uricemia (X-line) and uric acid clearance (Y-line)

Given the significant gender differences in the reference values of uricemia [20,22,24], they, as well as the norms of uricosuria and clearance, were recalculated on Z-scores (normalized). At the next stage, the sample was divided into quantitative and qualitative clusters (Fig. 5).

In 56 cases (45 men and 11 women), the values of renal clearance of uric acid were in the classical normal range: -1.97σ÷+1.74σ.

In 11 cases (5 men and 6 women), reduced clearance (-2.01σ÷-3.28σ), that is, a urate-retaining kidney, was established. Instead, 18 men and 3 women were diagnosed with a urate-losing kidney. In view of the "jumping" values of the clearance falling into the eyes in three cases (Figs. 3-4), they were allocated to a separate cluster. By the way, the problem of dropped values was considered by our group in a recent article, in which it was demonstrated that they are accompanied by anomalous deviations of a number of other parameters, that is, they are carriers of unique information, and not artifacts that should be discarded [17]. Spoiler: this will be confirmed in this article.

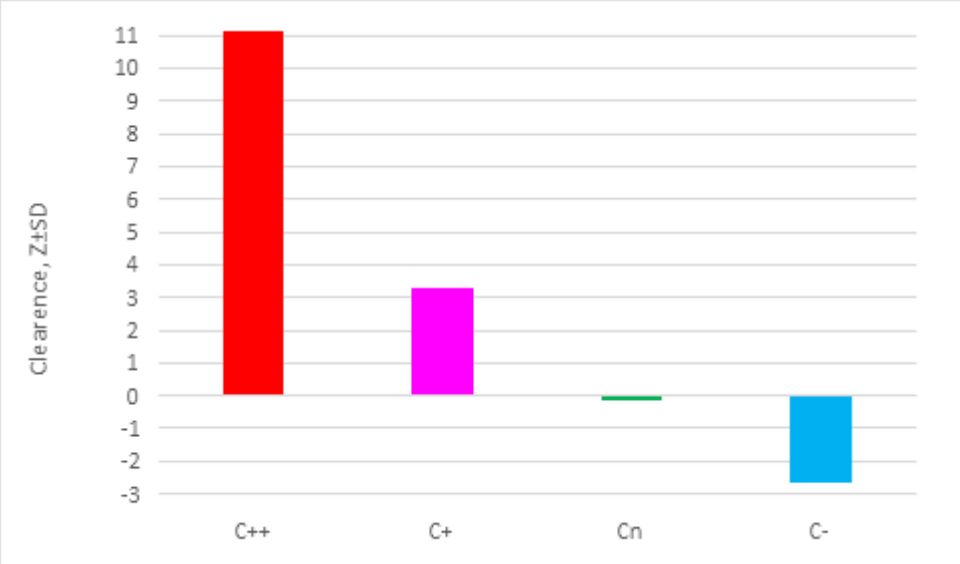


Fig. 5. Clusters of uric acid clearance

Screening of the registered parameters, previously recalculated on Z-scores [30], revealed those whose patterns to one degree or another are similar to the pattern of renal clearance of uric acid (Fig. 6, see also Table 5).

The constellation of uricosuria, diuresis, excretion of urea and calcium, as well as LF band HRV, were found to be the most similar, the levels of which were significantly reduced in cases of urate-retaining kidney, normal in cases of euuricosis, increased in cases of urate-losing kidney, and abnormally high in three separate cases. On the other hand, the constellation of 5 parameters of the second pattern (blood levels of uric acid, sodium, chloride, catalase, as well as Stange's test) is almost a mirror image. The remaining patterns are only partially similar or mirror the pattern of uric acid clearance.

Fig. 6. Patterns of neuro-endocrine-metabolic accompaniments of four clusters of uric acid clearance. ***Under each pattern the number of variables is indicated***

Discriminant analysis (method forward stepwise) [23] was used to identify the specific accompaniment of uric acid clearance. The discriminant model includes (Tables 1 and 2), in addition to **clearence, uricosuria and uricemia** by definition, 8 **autonomic-endocrine**, 2 **lipids peroxydation**, 9 **metabolic** variables, as well as Stange's test (spoiler: neural marker).

Table 1. Summary of discriminant function analysis

Step 23, N of vars in model: 23; Grouping: 4 grp; Wilks' Λ: 0,009; appro. $F_{(69,2)}$=10,4; $p<10^{-6}$

Variables currently in the model (Mean±SE)	Clusters of Uric Acid Clearance (M/F)				Parameters of Wilks' Statistics					
	C++ (2/1)	C+ (16/2)	Cn (45/11)	C- (5/6)	Wilks Λ	Partial Λ	F-remove (3,62)	p-level	Tolerancy	Norm Cv
Uric Acid Clearance, mL/min	27,0 2,2	13,33 0,35	7,68 0,27	3,65 0,22	0,049	0,182	93,19	10^{-6}	0,101	7,94 0,215
Uricosuria, mM/24 h	6,56 0,37	5,40 0,29	3,57 0,14	1,99 0,11	0,029	0,311	45,80	10^{-6}	0,074	3,00 0,250
Uricemia, µM/L	170 10	282 13	329 10	386 22	0,027	0,324	43,12	10^{-6}	0,095	263 0,181
RMSSD HRV, msec	40,3 7,2	30,5 4,1	28,4 2,4	23,8 3,3	0,010	0,849	3,67	0,017	0,032	28,8 0,486

pNN_{50} HRV, %	16,5 6,0	10,7 2,8	9,8 1,8	3,2 1,1	0,011	0,824	4,41	0,007	0,042	9,0 0,820
Total Power HRV, $msec^2$	6071 1608	2647 440	2544 282	1937 249	0,010	0,895	2,42	0,074	0,015	2379 0,402
ULF band HRV, $msec^2$	20 13	118 41	78 15	148 32	0,010	0,897	2,37	0,079	0,406	122 0,892
VLF band HRV, $msec^2$	2584 652	1085 173	1117 109	1145 182	0,010	0,870	3,10	0,033	0,065	1250 0,572
LF band HRV, $msec^2$	2785 736	1081 202	861 105	393 80	0,010	0,906	2,14	0,105	0,051	625 0,482
LFnu HRV, %	81,8 5,0	72,3 4,1	71,1 2,2	64,5 5,1	0,010	0,868	3,14	0,032	0,232	64,2 0,201
Calcitonin normalized, Z	-0,95 0,07	-0,64 0,18	-0,66 0,14	-0,43 0,23	0,011	0,809	4,89	0,004	0,593	0
Catalase, µM/L•h	37 10	88 11	123 7	134 20	0,010	0,904	2,19	0,098	0,289	125 0,458
Superoxide dismutase, U/mL	53 4	63 6	78 3	70 9	0,011	0,840	3,94	0,012	0,248	62 0,286
Urea Serum, mM/L	7,27 1,00	6,27 0,38	5,97 0,12	5,27 0,26	0,012	0,758	6,61	0,001	0,543	5,60 0,178
Calcium Serum, mM/L	2,12 0,08	2,20 0,05	2,18 0,02	2,30 0,06	0,009	0,952	1,04	0,382	0,515	2,30 0,065
Phosphates Serum, mM/L	0,98 0,11	1,01 0,05	1,00 0,02	1,14 0,08	0,009	0,937	1,39	0,254	0,442	1,20 0,167
Potassium Serum, mM/L	3,95 0,38	4,50 0,11	4,35 0,07	4,18 0,17	0,010	0,892	2,50	0,068	0,599	4,55 0,104
Diuresis, L/24h	2,87 0,07	2,52 0,15	1,88 0,08	1,41 0,20	0,010	0,924	1,70	0,177	0,208	1,40 0,274
Chloride Excretion mM/24h	316 49	263 23	212 13	186 34	0,011	0,822	4,48	0,007	0,341	167,5 0,172
Phosphates Excretion, mM/24h	27,4 7,4	32,0 3,6	23,0 2,1	14,1 2,8	0,009	0,939	1,35	0,266	0,449	25,2 0,294
Creatininuria, mM/24h	8,96 0,80	8,49 0,70	8,20 0,55	6,63 0,88	0,010	0,915	1,92	0,136	0,274	11,0 0,300
$(U•Ca)/(Cr•Mg)^{0,25}$ Lytogenicity Urine	1,00 0,04	0,94 0,04	0,84 0,02	0,72 0,03	0,010	0,915	1,92	0,136	0,290	0,73 0,255
Stange's test, sec	47 3	56 4	61 2	64 4	0,009	0,947	1,15	0,337	0,621	50 0,200

Table 2. Summary of forward stepwise analysis

Variables currently in the model	F to enter	p-level	Λ	F-value	p-level
Uric Acid Clearance, mL/min	160	10^{-6}	0,149	160	10^{-6}
Uricosuria, mM/24 h	8,63	10^{-4}	0,114	54,4	10^{-6}
Uricemia, µM/L	33,3	10^{-6}	0,051	53,1	10^{-6}
Calcitonin normalized by sex, Z	3,09	0,032	0,046	39,4	10^{-6}
$(UA•Ca)/(Cr•Mg)^{0,25}$ Lytogenicity	3,35	0,023	0,041	32,2	10^{-6}
Phosphates Excretion, mM/24h	3,32	0,024	0,036	27,8	10^{-6}
Urea Serum, mM/L	3,39	0,022	0,032	24,7	10^{-6}
Superoxide dismutase, U/mL	2,76	0,048	0,029	22,3	10^{-6}
VLF band HRV, $msec^2$	2,47	0,069	0,026	20,4	10^{-6}
Chloride Excretion mM/24h	2,05	0,115	0,024	18,7	10^{-6}
ULF band HRV, $msec^2$	1,95	0,129	0,022	17,4	10^{-6}
Total Power HRV, $msec^2$	1,75	0,165	0,021	16,2	10^{-6}
RMSSD HRV, msec	2,24	0,091	0,019	15,3	10^{-6}
pNN_{50} HRV, %	4,25	0,008	0,016	15,1	10^{-6}

Stange's test, sec	1,84	0,148	0,015	14,4	10^{-6}
LFnu HRV, %	2,21	0,095	0,014	13,8	10^{-6}
Potassium Serum, mM/L	1,50	0,222	0,013	13,2	10^{-6}
Catalase, µM/L•h	1,74	0,168	0,012	12,7	10^{-6}
Creatininuria, mM/24h	1,27	0,293	0,011	12,1	10^{-6}
Diuresis, L/24h	1,64	0,188	0,011	11,7	10^{-6}
LF band HRV, msec^2	1,55	0,211	0,010	11,3	10^{-6}
Phosphates Serum, mM/L	1,18	0,325	0,009	10,8	10^{-6}
Calcium Serum, mM/L	1,04	0,382	0,009	10,4	10^{-6}

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

Table 3. Variables currently not in the model

Variables (Mean±SE)	Clusters of Uric Acid Clearance (M/F)				Parameters of Wilks' Statistics					
	C++ (2/1)	C+ (16/2)	Cn (45/11)	C- (5/6)	Wilks Λ	Partial Λ	F to enter	p-level	Tolerancy	Norm Cv
TNN HRV, units	15,6 2,4	11,1 0,9	10,9 0,5	9,7 0,85	0,009	0,957	0,91	0,442	0,176	11,2 0,217
SDNN HRV, msec	79 11	48 4	47 3	44 3	0,009	0,985	0,32	0,813	0,040	56,2 0,516
PTH, pM/L	4,54 0,43	4,34 0,24	3,73 0,15	2,94 0,33	0,009	0,971	0,61	0,610	0,083	3,75 0,230
Aldosterone, pM/L	232 5	221 5	227 4	239 4	0,009	0,974	0,54	0,654	0,219	238 0,154
BP systolic, mmHg	150,1 2,1	146,8 4,6	135,6 2,3	143,6 7,0	0,009	0,994	0,12	0,946	0,056	124,5 0,122
BP diastolic, mmHg	95,2 4,4	87,8 2,9	81,2 1,2	80,3 2,5	0,009	0,962	0,79	0,502	0,442	79,0 0,083
Ps2/Ps1 Ratio	0,899 0,041	0,931 0,016	0,973 0,013	0,957 0,009	0,009	0,984	0,34	0,796	0,652	0,964 0,051
Pd2/Pd1 Ratio	1,013 0,019	1,010 0,015	0,994 0,010	0,983 0,021	0,009	0,977	0,49	0,693	0,661	0,965 0,051
Pd3/Pd1 Ratio	1,045 0,036	1,029 0,011	0,996 0,008	1,008 0,009	0,009	0,989	0,23	0,873	0,684	0,971 0,041
Diene conjugates, E^{232}/mL	1,83 0,01	1,67 0,04	1,51 0,02	1,50 0,07	0,009	0,977	0,49	0,691	0,059	1,90 0,279
Chloride Serum, mM/L	88,1 3,9	99,5 1,5	102,9 0,8	105,9 1,6	0,009	0,993	0,15	0,932	0,512	101,5 0,032
Sodium Serum, mM/L	125,8 4,9	140,0 1,9	144,3 1,1	148,0 1,9	0,009	0,976	0,49	0,690	0,367	145 0,034
Sodium Excretion, mM/24h	303 44	246 21	206 11	176 31	0,009	0,972	0,59	0,623	0,043	154 0,211
Calcium Excretion, mM/24h	8,22 1,20	6,24 0,72	4,84 0,39	3,45 0,94	0,009	0,966	0,72	0,546	0,259	4,38 0,214
Magnesium Excretion, mM/24h	6,11 0,83	5,46 0,46	4,49 0,26	3,72 0,51	0,009	0,983	0,36	0,784	0,302	4,10 0,266
Potassium Excretion, mM/24h	113 8	80 8	68 4	70 15	0,009	0,975	0,51	0,675	0,284	65 0,269
Urea Excretion, mM/24h	863 86	711 53	546 27	350 45	0,009	0,966	0,72	0,543	0,151	458 0,186

Following the algorithm [15,30,31], we transform the 23-dimensional space of discriminant variables into the 3-dimensional space of canonical roots. The canonical correlation coefficient for the first root is 0,965 (Wilks' Λ=0,009; $\chi^2_{(69)}$=347; $p<10^{-6}$), for the second 0,898 (Wilks' Λ=0,131; $\chi^2_{(44)}$=150; $p<10^{-6}$); for the third 0,572 (Wilks' Λ=0,673; $\chi^2_{(21)}$=29; p=0,110). The major root contains 74,7% of the discriminant possibilities, the minor – 22,6%, the last – 2,7% only.

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 (Fig. 7).

Table 4. Standardized and raw coefficients and constants for variables

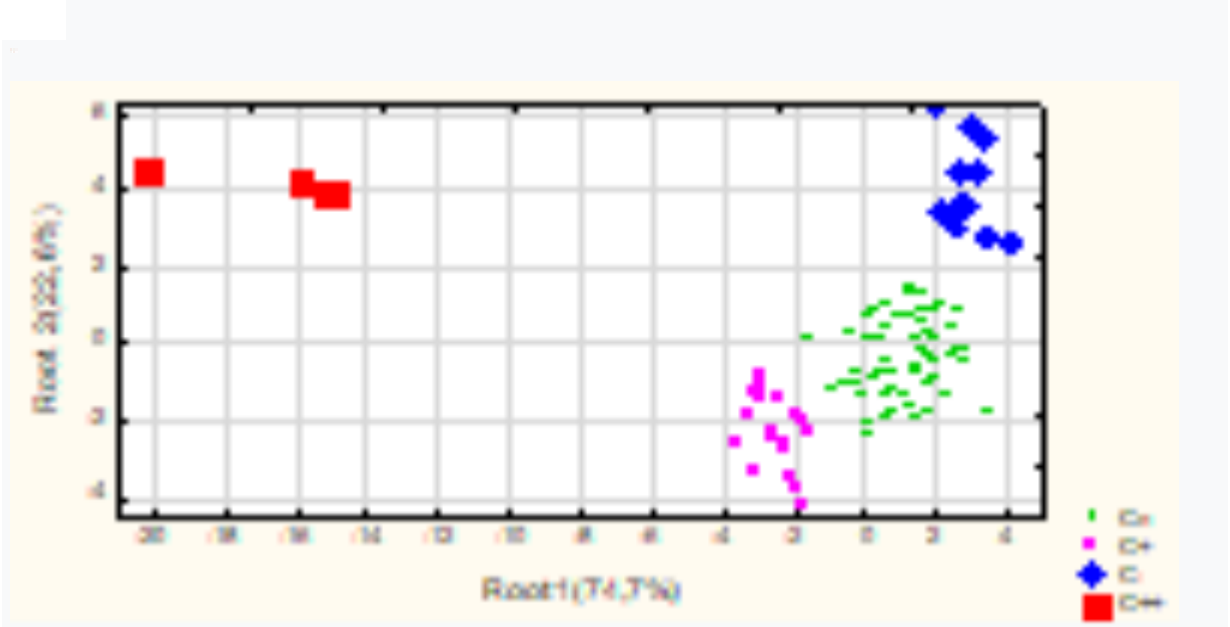
Coefficients	Standardized			Raw		
Variables	Root 1	Root 2	Root 3	Root 1	Root 2	Root 3
Uric Acid Clearance, mL/min	-2,387	1,851	-0,112	-1,258	0,975	-0,059
Uricosuria, mM/24 h	1,894	-2,706	0,615	1,828	-2,612	0,594
Uricemia, µM/L	-1,127	2,708	-0,394	-0,016	0,038	-0,006
Calcitonin normalized by sex, Z	0,585	0,014	0,105	0,669	0,016	0,120
(UA•Ca)/(Cr•Mg)^{0,25} Lytogenicity	-0,321	0,010	-0,774	-2,298	0,073	-5,545
Phosphates Excretion, mM/24h	-0,349	-0,161	0,084	-0,023	-0,011	0,006
Urea Serum, mM/L	0,073	-0,711	-0,323	0,066	-0,643	-0,292
Superoxide dismutase, U/mL	0,568	-0,541	-0,576	0,024	-0,023	-0,024
VLF band HRV, msec^2	-0,663	0,989	1,577	-0,0008	0,0013	0,0020
Chloride Excretion mM/24h	0,710	-0,238	-0,141	0,0073	-0,0025	-0,0015
ULF band HRV, msec^2	-0,098	-0,304	0,722	-0,0008	-0,0024	0,0057
Total Power HRV, msec^2	1,060	-0,602	-4,241	0,0005	-0,0003	-0,0022
RMSSD HRV, msec	1,688	1,349	1,380	0,098	0,078	0,080
pNN$_{50}$ HRV, %	-0,993	-1,992	-0,390	-0,080	-0,161	-0,032
Stange's test, sec	0,027	0,318	0,089	0,002	0,020	0,006
LFnu HRV, %	0,518	-0,598	-0,303	0,031	-0,036	-0,018
Potassium Serum, mM/L	0,284	-0,358	0,069	0,519	-0,654	0,126
Catalase, µM/L•h	-0,325	0,467	0,421	-0,0064	0,0093	0,0084
Creatininuria, mM/24h	0,201	-0,027	-0,911	0,054	-0,007	-0,244
Diuresis, L/24h	-0,453	-0,305	0,548	-0,727	-0,489	0,878
LF band HRV, msec^2	-1,070	0,360	1,423	-0,0014	0,0005	0,0018
Phosphates Serum, mM/L	-0,095	0,239	0,520	-0,474	1,195	2,607
Calcium Serum, mM/L	0,204	-0,259	-0,007	1,161	-1,470	-0,039
		Constants		2,498	-0,054	4,779
		Eigenvalues		13,70	4,147	0,487
	Cumulative Proportions			0,747	0,973	1

At the next stage of the analysis, the normalized values of the variables were 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 variables

Variables	Correlations Variables-Roots			C++ (2/1)	C+ (16/2)	Cn (45/11)	C- (5/6)
Root 1 (74,6%)	**R 1**	**R 2**	**R 3**	**-17,0**	-2,5	1,2	2,9
UA Clearance	**-0,628**	-0,266	0,098	**11,1±1,6**	3,25±0,17	-0,14±0,15	-2,63±0,11
Uricosuria	**-0,239**	-0,308	0,189	**4,75±0,50**	3,20±0,39	0,76±0,19	-1,35±0,15
Urea Excretion				**4,75±1,00**	2,97±0,62	1,03±0,32	-1,27±0,53
Diuresis	**-0,130**	-0,163	0,144	**3,82±0,18**	2,92±0,39	1,26±0,22	0,04±0,53

Calciuria				4,11±1,28	1,99±0,77	0,49±0,42	-0,99±1,01
LF band HRV	-0,138	-0,024	-0,188	8,56±1,15	2,06±0,80	0,45±0,29	-0,43±0,40
Parathyroid horm				0,92±0,50	0,68±0,28	-0,02±0,17	-0,94±0,38
Total Power HRV	-0,090	0,018	-0,171	4,51±1,28	0,50±0,47	-0,01±0,26	-0,10±0,38
VLF band HRV	-0,081	0,077	-0,125	2,08±0,79	-0,15±0,25	-0,25±0,14	0,00±0,31
pNN_{50} HRV	-0,042	-0,060	-0,137	1,34±0,84	0,43±0,42	0,01±0,23	-0,69±0,20
RMSSD HRV	-0,043	-0,024	-0,059	1,35±0,77	0,42±0,46	-0,22±0,13	0,14±0,39
SDNN HRV				0,90±0,32	-0,24±0,15	-0,37±0,08	-0,34±0,12
TNN HRV				1,83±0,98	-0,03±0,36	-0,13±0,22	-0,61±0,35
LFnu band HRV	-0,042	-0,038	-0,112	1,31±0,39	0,61±0,32	0,57±0,17	-0,06±0,40
Lytogenicity Urine	-0,101	-0,160	0,007	1,41±0,22	1,11±0,22	0,58±0,10	-0,08±0,17
Magnesiuria				1,91±0,79	1,29±0,43	0,37±0,25	-0,36±0,49
Urea Serum	-0,080	-0,074	-0,124	1,51±0,57	0,63±0,37	0,41±0,13	-0,33±0,29
BP diastolic				2,48±0,67	1,34±0,44	0,33±0,18	0,19±0,38
Pd2/Pd1 Ratio				0,98±0,38	0,90±0,30	0,58±0,20	0,36±0,43
Chloriduria	-0,073	-0,062	0,055	5,16±1,69	3,31±0,80	1,84±0,43	0,65±1,21
Natriuria				4,58±1,36	2,83±0,64	1,60±0,34	0,66±0,97
Kaliuria				2,77±0,48	0,85±0,44	0,18±0,25	0,27±0,89
Creatinineuria	-0,024	-0,058	-0,087	-0,62±0,24	-0,76±0,21	-0,85±0,17	-1,32±0,27
Diene conjugates				-0,14±0,01	-0,44±0,07	-0,73±0,04	-0,75±0,14
Uricemia	0,147	0,105	0,063	-1,89±0,32	0,30±0,26	1,31±0,19	2,94±0,37
Catalase	0,108	0,046	-0,139	-1,54±0,18	-0,65±0,19	-0,04±0,12	0,16±0,35
Chloride Serum				-4,13±1,20	-0,63±0,46	0,42±0,26	1,34±0,48
Sodium Serum				-3,90±0,99	-1,01±0,38	-0,15±0,21	0,61±0,40
Stange's test	0,055	0,030	0,005	-0,33±0,34	0,65±0,44	1,05±0,21	1,43±0,42
ULF band HRV	0,024	0,020	0,300	-0,94±0,12	-0,04±0,38	-0,40±0,14	0,24±0,30
Calcium Serum	0,030	0,069	0,238	-1,20±0,55	-0,69±0,30	-0,80±0,15	0,02±0,39
Phosphates Serum	0,019	0,083	0,229	-1,07±0,54	-0,92±0,23	-1,02±0,17	-0,29±0,40
Calcitonin norm-d	0,019	0,012	0,087	-0,95±0,07	-0,64±0,16	-0,66±0,15	-0,43±0,26
Root 2 (22,6%)	**R 1**	**R 2**	**R 3**	4,2	-2,3	-0,3	4,2
Phosphaturia	-0,053	-0,139	0,090	0,30±0,99	0,92±0,49	-0,30±0,29	-1,50±0,38
Potassium Serum	0,013	-0,101	0,089	-1,28±0,80	-0,10±0,24	-0,42±0,16	-0,78±0,37
Aldosterone				-0,15±0,14	-0,46±0,14	-0,30±0,11	0,04±0,12
Root 3 (2,7%)	**R 1**	**R 2**	**R 3**	-0,9	1,0	-0,4	0,9
Superoxidedismut	0,062	-0,012	-0,295	-0,50±0,24	0,08±0,34	0,92±0,17	0,43±0,51
Ps2/Ps1 Ratio				-1,72±0,82	-1,08±0,31	-0,24±0,25	-0,56±0,18
BP systolic				1,68±0,14	1,47±0,31	0,73±0,15	1,26±0,46
Pd3/Pd1 Ratio				1,86±0,91	1,47±0,27	0,62±0,20	0,92±0,23



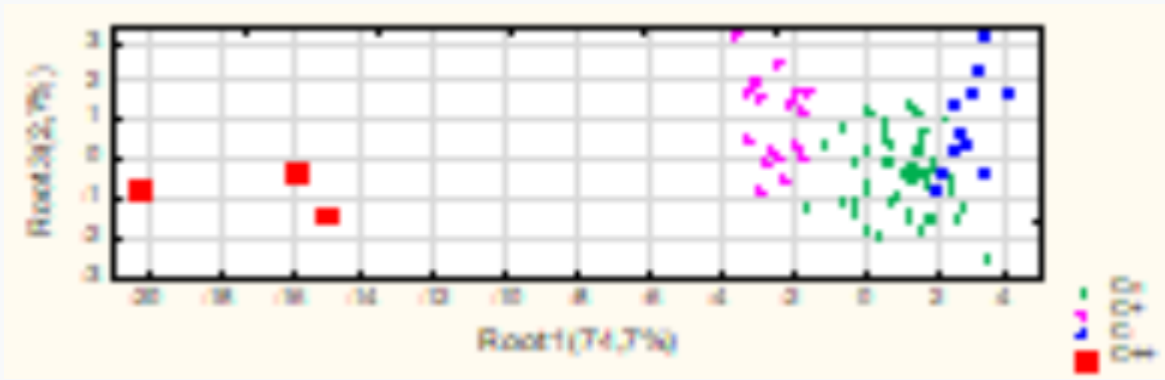


Fig. 7. Scattering of individual values of the discriminant roots of patients from different clusters of uric acid clearence

Localization of individual values of the first discriminant root visualizes abnormal deviations from the norm, along with clearance, uricosuria and uricemia by definition, a number of other metabolic and autonomic-endocrine parameters. Patients with a moderately urate-losing kidney are also moderately distant from patients with a euuricosic kidney, but their demarcation is clear. At the same time, patients with urate-retaining kidneys are not clearly demarcated.

However, these two clusters are clearly demarcated along the second root axis. The top position of patients with urate-retaining kidneys reflects their minimum levels of phosphaturia and kaliemia, as well as a normal, but maximum for the sample, aldosterone level. The lowest localization of patients with urate-losing kidney reflects their maximum phosphaturia and normal, but maximum for the sample, serum potassium level, as well as the lowest aldosterone level. Euuricose patients occupy an intermediate position.

Additional demarcation of patients with euuricosis occurs along the axis of the third root. Their lowest position reflects their highest SOD activity. Euuricosis is accompanied by a normal level of diastolic pressure and its reactions to occlusion during the triplex tensiometric test [32]. Instead, these parameters are higher/lower, respectively, in patients with clearance deviations from the norm.

In general, in the information space of the three roots, the demarcation of clusters is quite clear, which is documented by the calculation of Mahalanobis distances (Table 6).

Table 6. Mahalanobis distances between clusters, F-values (df=23,6) and p-levels

Clus-ters	Cn	C+	C-	C++
Cn	0	20	25	352
C+	8,6 10^{-6}	0	71	257
C-	7,4 10^{-6}	15,6 10^{-6}	0	399
C++	32,2 10^{-6}	21,2 10^{-6}	30,2 10^{-6}	0

With the help of classification functions coefficients and constants (Table 7), we will find out the possibility of identifying the belonging of this or that person to this or that cluster without errors.

Table 7. Coefficients and constants for cluster classification functions

Clusters	Cn	C+	C-	C++
Variables	p=,636	p=,205	P=,125	p=,034
Uric Acid Clearence, mL/min	4,789	7,379	6,977	32,138
Uricosuria, mM/24 h	-16,08	-16,73	-23,93	-61,45
Uricemia, µM/L	0,117	0,091	0,254	0,580
Calcitonin normalized, Z	-2,393	-4,710	-1,025	-14,543
Lytogenicity urine	74,17	74,53	62,85	118,6
Phosphates Excretion, mM/24h	-0,764	-0,649	-0,843	-0,392
Urea Serum, mM/L	11,85	12,47	8,650	7,853
Superoxide dismutase, U/mL	0,440	0,363	0,343	-0,089
VLF band HRV, msec^2	-0,057	-0,054	-0,050	-0,037
Chloride Excretion mM/24h	0,057	0,033	0,056	-0,088
ULF band HRV, msec^2	-0,080	-0,064	-0,084	-0,079
Total Power HRV, msec^2	0,053	0,048	0,049	0,042
RMSSD HRV, msec	1,969	1,568	2,597	0,512
pNN_{50} HRV, %	-2,591	-2,019	-3,496	-1,845
Stange's test, sec	0,725	0,687	0,825	0,781
LFnu HRV, %	1,394	1,326	1,260	0,676
Potassium Serum, mM/L	30,13	29,71	28,24	17,67
Catalase, µM/L•h	-0,126	-0,109	-0,084	0,030
Creatininuria, mM/24h	1,615	1,082	1,331	0,704
Diuresis, L/24h	11,35	16,26	9,150	22,01
LF band HRV, msec^2	-0,074	-0,067	-0,071	-0,047
Phosphates Serum, mM/L	-16,26	-13,17	-8,021	-3,272
Calcium Serum, mM/L	106,94	105,5	102,2	79,09
Constants	-362,0	-370,8	-365,4	-566,4

DISCUSSION

Urate handing in the human body is a complex system including three major processes: production, renal elimination, and intestinal elimination. A change in any one of these can affect both the steady-state serum urate concentration as well as other urate processes. The remarkable complexity underlying urate regulation and its maintenance at high levels in humans suggests that this molecule could potentially play an interesting role other than as a mere waste product to be eliminated as rapidly as possible. Urate is produced during the metabolism of endogenous (typically DNA and RNA) and exogenous (food-derived) purines. Once produced, urate cannot be further metabolized by human cells and so must be eliminated by either renal or extra-renal elimination routes [19]. The kidney excretes two-thirds of UA. Skin, nails, hair, saliva, and the gastrointestinal tract (GIT) eliminates the remaining third. In the GIT, bacteria convert part of the uric acid to ammonia and carbon dioxide, which is expelled as gas. Ammonia is either absorbed and excreted in the urine or utilized by bacteria as an energy source. The majority of serum UA (95%) is in the form of monosodium urate and is freely filtered at in the glomeruli, while the remaining is protein bound. Ninety-nine percent of the filtered urate is reabsorbed in the proximal convoluted tubule (PCT) through complex successive reabsorption, secretion, and again reabsorption and 50% is then secreted back into the PCT. Post secretory absorption of 80% of this urate occurs in the distal PCT. Therefore, about 10% of the filtered urate is excreted in the urine. The fractional excretion of urate ranges from 60% in a premature neonate, to 12% in a children and 7% in the adults [1].

The balance of production and elimination determines the concentration of urate in the circulation. Urate, with a pKa of 5.3, is also found in its deprotonated form uric acid;

however, uric acid represents only ~1% of the total urate in blood because of the pH. In urine, more of the urate is unprotonated uric acid due to the lower pH found in urine but at any urine pH above 5.3, more than half the molecule will be in the form of urate. Elevated serum urate (sUA) is the primary cause of gout, an inflammatory arthritis induced by monosodium urate crystals. Hyperuricemia is defined as sUA concentrations greater than 404 μmol/L, which is the in vitro solubility limit of monosodium urate. Gout occurs in patients with sUA above 404 μmol/L and gout prevalence increases as sUA rises above the 404 μmol/L threshold. International guidelines recommend lowering sUA levels to a target range of <360 μmol/L in all gout case scenarios and below <300 μmol/L in those with greater disease severity and urate burden, such as those with tophi. Therefore, clarity on the interplay between factors that affect serum urate handling is a key component to understanding and treating gout [19].

Elimination of urate occurs via two routes: renal elimination and extra-renal elimination. Urate elimination is a dynamic process mediated by multiple specific import and export transporters in the renal proximal tubule, salivary glands and the intestinal mucosa. The amount of urate excreted via these elimination routes can be quantified as clearance in milliliters per minute of serum (or blood) in the circulation that is cleared. Thus, the total clearance of urate is the sum of the renal clearance and the extra-renal clearance. The total rate of urate removed per minute is the product of the total clearance and the sUA concentration. So, at steady state, for a given rate of production, sUA will settle at a point at which total elimination is equal to production. These relationships form the basis for understanding the dynamics of urate concentration in the serum. The kidney is typically responsible for approximately 60–65% of daily urate elimination. Urate in blood is freely filtered in the kidney by the glomerulus. The filtered urate is subjected to significant reabsorption in the proximal tubule. In addition, secretion of urate also occurs. Both these processes are carried out by a series of membrane transporters. Of the filtered urate, only 3–10% is eventually excreted in the urine with the majority reabsorbed in the proximal tubule [19].

CONCLUSION

Constitutionally distinct types of uric acid metabolism (euricosis, urate losing and saving kidneys) are characterized by specific constellations of metabolic and autonomic-endocrine parameters. A detailed analysis of the mechanisms of such connections will be carried out in the next article.

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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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