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INFLUENCE BALNEOTHERAPY ON SPA TRUSKAVETS' WITH TAKING CANEPHRON® N ON URINA LITHOGENICITY AND ITS METABOLIC AND NEUROENDOCRINE-IMMUNE ACCOMPANIMENTS IN PATIENTS WITH CHRONIC PYELONEPHRITE AND CHOLECYSTITE

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SUMMARY

Objective. We know that balneotherapy on spa Truskavets' did not significantly affect the parameters of urina Lithogenicity, including Ca/Mg ratio, so search for means of reducing urina Lithogenicity remains relevant. We also know that Phytopreparation Canephron® N recommended for inclusion in complex therapy of chronic pyelonephrite as effective elimination of infectious kidney inflammation, prevention of recurrence of inflammation and lithogenese. **Aim:** to find out the possibility of reducing urina Lithogenicity influenced balneotherapy on spa Truskavets' by additional taking Canephron® N. **Results.** Standardized balneotherapy not significantly affect urina Lithogenicity in patients with chronic pyelonephrite and cholecystite, even showed a trend to increase, while additional use Canephron® N significantly reduces urina Lithogenicity by reducing the concentration of Uric acid and downward trend Calcium. Reducing urina Lithogenicity accompanied by a decrease urina concentration Chloride and Potassium, and Baevskiy's Activity Regulatory Systems Index, Asymmetry δ-, θ- and α-rhythms of background EEG and α-rhythm normalized Power Spectrum Density (PSD) in right loci Fp2, F8, T6 and O2, while HRV markers of vagal tone (RMSSD, pNN_{50}, TI) also Frequency Deviation θ- and β-rhythms, Amplitude β- and δ-rhythms, δ-rhythm PSD in loci Fp2, F8, T3, T5, O1, O2, β-rhythm PSD in loci Fp1, F4 and θ-rhythm PSD in loci T3 and F7 rising. However, Canephron® N preventes or reverses increasing Uric acid plasma level, Mineralocorticoide Activity, Sympathetic tone, Baevskiy's Stress Index and PSD ULF HRV also decreasing PSD VLF HRV. Concerning parameters of Immunity Canephron® N decreases blood level active T-Lymphocytes but increases level B-Lymphocytes, Stubnucleary Neutrophiles and total Leukocytes also prevents or reverses increasing $CD16^+$ NK-Lymphocytes, $CD8^+$ and

Theophilinesensitive T-Lymphocytes, Monocytes and serum IgM also decreasing $CD4^+$ T-Lymphocytes and Neutrophiles Phagocytose Count vs Staphylococcus aureus. In addition, Canephron® N potentiates increasing Parathyrine Activity, serum level IgG and Bactericidic Capacity of Neutrophiles vs Staphylococcus aureus also decreasing Urea and Creatinine plasma level, Sodium urina concentration and Neutrophiles Phagocytose Count vs Escherichia coli. **Conclusion.** Introduce Canephron® N into standard balneotherapeutic complex spa Truskavets' contribute to decrease urina Lithogenicity accompanied by decreasing of HRV and EEG markers of chronic Stress and favorable modulation parameters of Immunity in patients with chronic pyelonephrite and cholecystite.

Keywords: lithogenicity of urina, EEG, HRV, immunity, spa Truskavets', Canephron® N.

INTRODUCTION

We have previously analyzed the links urina Lithogenicity in patients with chronic pyelonephrite and cholecystite with a concentration in urine and plasma electrolytes and nitrogenous metabolites and the parameters Gall-bladder Motility, HRV, EEG and Immunity. Revealed significantly correlation urina Lithogenicity with Uric acid Plasma level and Gall-bladder postprandial Volume, Baevskiy's Stress Index, Sympatho-Vagal Balance Index HRV, δ-rhythm amplitude, α-rhythm frequency and θ-rhythm asymmetry index EEG, blood levels of $CD19^+$ B-Lymphocytes and $CD16^+$ NK-Lymphocytes. Canonical correlation between urina Lithogenicity and Neuro-Humoral-Immune factors is veri strong: R=0,97 [12]. It has long been known that balneotherapy on spa Truskavets' did not significantly affect the Ca/Mg ratio of urina (before 1,9±0,2, after 1,8±0,2) [30]. Uric acid/Creatinine ratio of urina different groups of patients respond to balneotherapy ambiguous (0,61±0,09 and 0,43±0,11 in 6; 0,65±0,06 and 0,42±0,03 in 36; 0,65±0,13 and 0,23±0,03 in 15; 0,36±0,11 and 0,63±0,05 in 5 before and after balneotherapy respectively while the normal average is 0,22±0,02) [14]. This is due, perhaps, ambiguous influence balneotherapy on the parameters of neuroendocrine-immune complex and metabolism [2,5-7,13,14,16,17,24]. We found that the Ca/Mg ratio of urina increased in 29,3% patients of spa Truskavets' with chronic pyelonephrite, some more in 63,2% persons it is on the upper limit of normal or somewhat exceeds it [10]. Thus, the search for means reduction urina Lithogenicity remains relevant. We opted for herbal remedies **Canephron® N.** He has combined neuroprotective, anti-inflammatory, diuretic, antispasmodic, vasodilatory and anti-bacterial action in children with renal tubulointerstitial lesions [15]**.** The inclusion of the drug in the treatment of chronic calculous pyelonephritis is effective in elimination of infectious inflammatory process in the kidneys, preventing recurrence of pyelonephritis and re-stone formation [29]**.** Amid drug use observed most expressive and positive dynamics bladder syndrome (decrease leukocyturia tripled bacteriuria – 2,7 times), peripheral blood parameters (normalization of leukocyte count, erythrocyte sedimentation rate, reducing C-reactive protein - in 1,3 times) [9]**.** Canephron® N is appropriate and safe drug recommended to restore immune and antioxidant status after antibiotic therapy in active stage pyelonephrite and antirelapse event in remission in all patients with pyelonephrite [19].

MATERIALS AND METHODS

The object of observation were 24 men aged 24-70 (mean 50±2) years, who were treated at the spa Truskavets' from chronic pyelonephritis, combined with cholecystitis in remission. In the morning on an empty stomach electrocardiogram recorded in II lead to assess the parameters of HRV [1] (software and hardware complex "KardioLab+HRV" production "KhAI-MEDICA" Kharkiv) and background electroencephalogram in 16 monopolar leads (software and hardware complex "NeuroCom" the same production). Details are given in our previous articles [26,27].

On the tone and motility of gall-bladder, that subordinates neuro-humoral influences, judged by its volume on an empty stomach in the morning and after 5, 15 and 30 min after ingestion cholekinetic (50 ml of 40% solution of xylitol). The method echoscopy (echocamera "Radmir") applicated [21].

About phagocytic function of neutrophils judged by activity (percentage of neutrophils, in which found microbes - Phagocytic index), intensity (number of microbes absorbed one phagocytes - Microbial

count) and completeness (percentage of dead microbes - Killing index) phagocytosis museum cultures Staphylococcus aureus (ATCC N 25423 F49) and Escherichia coli (O55 K59) from laboratory Truskavetsian hydrogeological regime-operational station [8,16].

Immune status evaluated on a set of I and II levels recommended by the WHO. For phenotyping subpopulations of lymphocytes used the methods of rosette formation and indirect immunofluorescent binding reaction monoclonal antibodies [22] from company "Sorbent" (RF) with visualization under fluorescent microscope. T-cellular immunity assessed by the following parameters: blood levels of a subpopulation of “active”, theophiline resistance and sensitive T-lymphocytes and T-lymphocytes phenotype of $CD3^+CD4^+$(helpers/inductors). State of killer link of immunity estimated by the content of $CD3^+CD8^+$-lymphocytes (T-killers) and $CD16^+$-lymphocytes (natural killers). The state of humoral immunity judged by the content of EAC and $CD19^+$ B-lymphocytes and concentration in serum of immunoglobulins classes G, A, M (radial immunodiffusion method) and circulating immune complexes (with polyethylene glycol precipitation method), using standardized methods described in manual [18].

In the urine collected during the day, determined oxalate content and nitrogen metabolites: creatinine, urea and uric acid, electrolytes: phosphates, chloride, calcium, magnesium, potassium and sodium. Nitrogenous metabolites in plasma of venous blood were determined also. Used unified methods [11].

In addition, registered the delay in breath (Stange’s Test) as a marker of resistance to hypoxia [16].

Testing was performed twice - at admission and after 10-12 days standard balneotherapy (drinking bioactive water Naftussya 3 ml/kg three times a day; application of ozokerite on the lumbar region, t 45ºC, lasting 20-30 minutes, every other day; baths mineral, concentration $Cl^-SO_4^{2-}Na^+Mg^{2+}$ salt 20-30 g/l, tº 36-37ºC, duration 8-10 minutes every other day) [16,23,25] or with the additional taking Canephron® N according to the instruction.

Results processed by methods of correlation, canonical and discriminant analyses, using the software package "Statistica 5.5".

RESULTS AND DISCUSSION

Lithogenicity Index (Lith) urine was calculated using the formula HS Tiselius [31] with our modification [12]:

$$Lith=(Oxalates \bullet Uric\ acid \bullet Calcium/Magnesium \bullet Creatinin)^{0,2}.$$

Fig. 1 shows that changes Lith ambiguous as in the Control, as well as in Experimental Groups, but with the additional taking Canephron® N dominated decreases Lith.

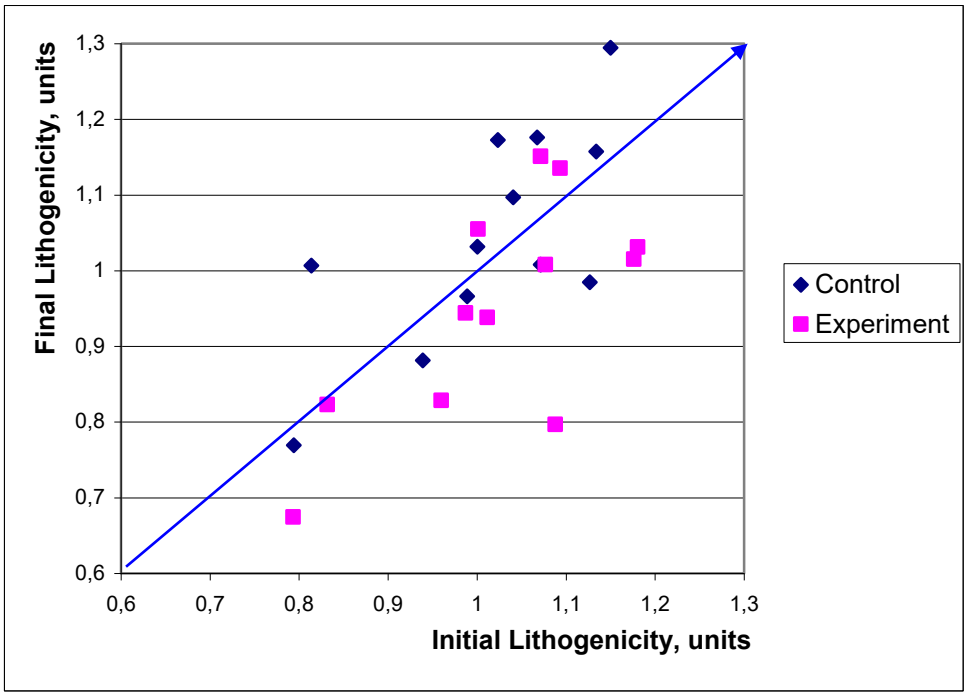

Fig. 1. Personal initial and final indexes of Lithogenicity in patients of Control and Experimental groups

The visual impression is confirmed by calculating Means of initial and final indexes (Fig. 2).

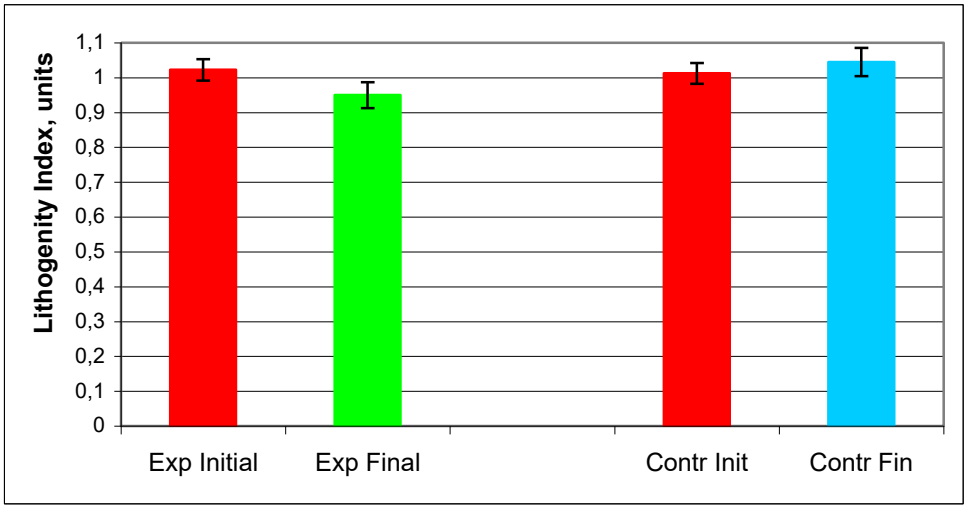

Fig. 2. Means of initial and final indexes of Lithogenicity in patients of Experimental and Control groups

Analysis of changes in individual components of the formula HS Tiselius [31] shows that additional taking Canephron® N significantly reduces urina Lithogenicity by reducing the concentration of Uric acid and downward trend Calcium, that is lithogenic substances (Table 1).

Table 1. Changes in urine concentration lipolytic and lithogenic substances in patients in the Control and Experimental groups

Groups	n		Lithoge-nicity	Creatinine, mM/l	Magnesium, mM/l	Oxalates, mM/l	Uric acid, mM/l	Calcium, mM/l
Before therapy (Basal level)	23	M m	1,015 0,024	3,02 0,15	2,39 0,11	1,10 0,13	2,00 0,12	2,69 0,29
After standard therapy (Control)	12	M m Δ mΔ	1,045 0,041 +0,033 0,029	2,80 0,22 -0,21 0,23	2,16 0,18 -0,24 0,21	0,61 0,14 -0,49 0,22*	2,14 0,14 +0,14 0,15	2,81 0,31 +0,13 0,18
After combined therapy (Experiment)	12	M m Δ mΔ	0,950 0,042 -0,073 0,031*#	3,18 0,54 +0,17 0,20	1,99 0,18 -0,40 0,22	0,61 0,09 -0,47 0,18*	1,69 0,16 -0,31 0,05*#	2,42 0,28 -0,28 0,18

Notices: M – Mean; m- its Standard Error; Δ- Change in Mean; mΔ - its Standard Error. Significant differences between the values Before and After balneotherapy* and between the Control and Experimental groups#

Accompanied changes metabolic parameters of urine and blood, as well as EEG, HRV and Immunity were grouped into a number of patterns (Tables 2-7). The changes expressed in Z-scores, that take into account the variability (Cv) of parameters before treatment. Significant believed Z-scores over 0,5 σ.

Table 2. Parameters independent of action standard balneotherapy, but falling under the influence Canephron® N

Gr-ps/Par-s	CCl_U, mM/l	CK_U, mM/l	ARSI (orth.)	Active T-L,%	EEG rhythms asymmetry, %			Normalized PSD of α-rhythm (%) in locus					
					δ	θ	α	T6	O2	Fp2	F8		
Before	103	37,7	4,7	28,6	41,5	30,3	17,4	37,7	52,0	37,6	30,1		
Cv	0,263	0,479	0,699	0,169	0,518	0,607	0,695	0,520	0,372	0,352	0,593		
Control	109	38,4	5,4	27,9	40,3	31,2	23,7	31,2	45,4	32,5	27,1	**Z**	**m**
(C/B-1)/Cv	0,24	0,04	0,23	-0,14	-0,05	0,05	0,52	-0,33	-0,34	-0,38	-0,17	**-0,03**	**0,09**
Experiment	81	29,7	3,2	25,2	27,6	18,0	10,0	24,3	38,3	24,0	19,0	**Z**	**m**
(E/B-1)/Cv	-0,82	-0,44	-0,46	-0,71	-0,65	-0,67	-0,61	-0,68	-0,71	-1,02	-0,62	**-0,67**	**0,05**

Table 3. Parameters independent of action standard balneotherapy, but rising under the influence Canephron® N

Gr-ps/Par-s	Ampl. δ, μV	Ampl. β, μV	Deviat. β, Hz	Fp2-δ, %	F8-δ, %	T3-δ, %	O1-δ, %	O2-δ, %	T5-δ, %	T3-θ,%	Fp1-β,%	F4-β, %	RMSSD HRV, ms	pNN_{50} HRV, %
Before	13,9	12,1	1,29	20,3	29,3	26,3	18,7	19,0	21,8	10,4	31,2	26,2	29,2	9,4
Cv	0,575	0,244	0,363	0,744	0,852	0,784	0,956	0,907	1,157	0,586	0,454	0,452	0,667	1,498
Control	16,1	12,0	1,28	23,2	26,4	29,1	19,5	19,1	23,6	8,1	36,2	30,6	35,0	12,5
(C/B-1)/Cv	0,27	-0,04	-0,03	0,19	-0,12	0,14	0,04	0,01	0,07	-0,37	0,35	0,37	0,30	0,22
Experiment	20,6	14,0	1,57	27,2	40,3	47,6	29,2	34,9	34,7	14,2	40,5	33,5	40,1	17,7
(E/B-1)/Cv	0,84	0,62	0,59	0,46	0,44	1,03	0,59	0,92	0,51	0,63	0,65	0,61	0,56	0,59

Extension of Table 3

Gr-ps/Par-s	Stange test, s	EAC B-L, %	CD19 B-L, %	Stubnucl. Neut., %			HRV TI, units	F7-θ, %	Frequens θ, Hz	Deviation θ, Hz	Leuk, 10^9/l		
Before	58,7	23,4	23,8	2,5			10,16	7,9	6,5	0,91	5,54		
Cv	0,371	0,237	0,103	0,356			0,442	0,512	0,192	0,522	0,223		
Control	56,0	23,5	24,0	2,3	**Z**	**m**	10,13	7,2	6,3	0,83	5,21	**Z**	**m**
(C/B-1)/Cv	-0,12	0,02	0,07	-0,24	**0,07**	**0,05**	-0,01	-0,19	-0,13	-0,16	-0,26	**-0,15**	**0,04**
Experiment	70,7	25,9	24,9	2,9	**Z**	**m**	11,75	9,2	6,9	1,07	5,78	**Z**	**m**
(E/B-1)/Cv	0,55	0,46	0,44	0,45	**0,60**	**0,04**	0,35	0,30	0,34	0,34	0,20	**0,31**	**0,03**

The first pattern (Table 2) shows that reducing urina Lithogenicity accompanied by a decrease urina concentration Chloride and Potassium, as well as Baevskiy's Activity Regulatory Systems Index, Asymmetry δ-, θ- and α-rhythms of background EEG and α-rhythm normalized Power Spectrum Density (PSD) in right loci Fp2, F8, T6 and O2, while (Table 3) HRV markers of vagal tone (Triangulary Index – TI, RMSSD, pNN_{50}) also Frequency Deviation θ- and β-rhythms, Amplitude β- and δ-rhythms, δ-rhythm PSD in loci Fp2, F8, T3, T5, O1, O2, β-rhythm PSD in loci Fp1, F4 as well as θ-rhythm PSD in loci T3 and F7 rising. However, Canephron® N prevents or reverses increasing Uric acid plasma level, urina K/Na ratio as marker of Mineralocorticoide Activity, Sympathetic tone, Baevskiy's Stress Index and PSD ULF HRV as well as decreasing PSD VLF HRV (Table 4).

Thus, reducing Lithogenicity associated with vagotonic shift of sympatho-vagal balance associated in turn with modulation parameters EEG [26,27]. This is consistent with the provisions of the role of Stress in urina Lithogenicity [3,4] as well as stresslimiting properties of Phytopreparations [7,16,23].

Concerning parameters of Immunity Canephron® N decreases blood level "active" T-Lymphocytes but increases level B-Lymphocytes, Stubnucleary Neutrophiles and total Leukocytes (Table 3) as well as prevents or reverses increasing $CD16^+$ NK-Lymphocytes, $CD8^+$ and Theophilinesensitive T-Lymphocytes, Monocytes and serum IgM (Table 4) also decreasing $CD4^+$ T-Lymphocytes and Neutrophiles Phagocytose Count vs Staphylococcus aureus (Table 5). Apparently discovered immunomodulation caused by neurogenic [17,23,28].

Table 4. Options boost which influenced the standard balneotherapy Canephron® N preventes or reverses

Gr-ps/Par-s	EK_U, mM/d	ECl_U, mM/d	$(K/Na)^{0,5}$, units	$Urat_P$, mM/l	PS ULF HRV, %	Fp1-δ, %	F4-δ, %	T3-β, %	C3-δ, %	P3-δ, %	O2-β, %	CD16 NK-L, %	CD8 T-L, %
Before	80,5	224	0,56	0,32	2,04	17,5	18,7	26,9	19,0	14,91	22,98	10,5	26,3
Cv	0,482	0,306	0,239	0,287	1,571	0,639	0,739	0,537	0,605	0,741	0,552	0,212	0,145
Control	102,8	290	0,64	0,38	4,38	25,7	31,2	35,4	25,1	23,51	30,34	12,2	28,4
(C/B-1)/Cv	0,57	0,96	0,65	0,64	0,73	0,73	0,91	0,59	0,54	0,78	0,58	0,77	0,55
Experiment	81,0	223	0,59	0,30	2,18	15,9	19,7	20,5	19,0	18,4	22,1	9,8	24,6
(E/B-1)/Cv	0,01	-0,02	0,26	-0,20	0,05	-0,15	0,08	-0,44	0,01	0,32	-0,07	-0,33	-0,44

Extension of Table 4

Gr-ps/Par-s	IgM, g/l	Mono-cytes, %			F8-β, %	O1-θ, %	C4-δ, %	Stress Index	AMo HRV, %	ARSI, units	Theo. Sensit. T-Lymph, %		
Before	1,33	7,0			30,6	6,05	18,7	4,90	44,9	3,9	23,5		
Cv	0,240	0,254			0,569	0,775	0,598	0,160	0,280	0,695	0,218		
Control	1,49	8,2	**Z**	**m**	39,2	8,03	23,2	5,17	48,4	4,9	25,6	**Z**	**m**
(C/B-1)/Cv	0,50	0,67	**0,68**	**0,03**	0,49	0,42	0,40	0,35	0,28	0,36	0,42	**0,39**	**0,03**
Experiment	1,42	6,4	**Z**	**m**	31,4	6,6	16,7	4,72	40,9	2,8	20,4	**Z**	**m**
(E/B-1)/Cv	0,28	-0,33	**-0,07**	**0,06**	0,04	0,11	-0,18	-0,22	-0,32	-0,42	-0,61	**-0,23**	**0,10**

Table 5. Options reduction which influenced the standard balneotherapy Canephron® N prevents

Gr-ps/Par-s	PS VLF HRV, %	α-rhythm Index, %	F4-α, %	C3-α,%	P3-α,%	T6-θ, %	0-Lympho-cytes, %	Microb. Count vs Staph. aur.		
Before	41,16	62,5	43,1	45,3	52,69	8,4	38,3	64,0		
Cv	0,468	0,427	0,420	0,409	0,359	0,549	0,150	0,135		
Control	31,44	44,6	29,1	35,6	42,63	4,8	35,3	59,2	**Z**	**m**
(C/B-1)/Cv	-0,50	-0,67	-0,77	-0,53	-0,53	-0,79	-0,52	-0,56	**-0,61**	**0,04**
Experiment	42,08	63,3	34,4	42,9	52,3	7,9	40,5	61,4	**Z**	**m**
(E/B-1)/Cv	0,05	0,03	-0,48	-0,13	-0,02	-0,10	0,38	-0,30	**-0,07**	**0,09**

Extension of Table 5

Gr-ps/Par-s	C4-α, %	F8-θ, %	T3-α, %	T4-θ, %	P4-θ, %	F4-θ, %	Fp2-θ,%	F3-α, %	CD4 T-L, %		
Before	44,1	10,0	36,5	10,9	8,81	12,0	10,0	41,4	24,9		
Cv	0,381	0,596	0,554	0,783	0,688	0,886	1,041	0,511	0,118		
Control	36,0	7,3	27,3	7,2	6,77	9,0	6,5	32,1	24,1	**Z**	**m**
(C/B-1)/Cv	-0,48	-0,45	-0,45	-0,44	-0,34	-0,28	-0,33	-0,44	-0,28	**-0,39**	**0,03**
Experiment	41,1	9,3	34,4	9,2	8,8	12,4	8,7	37,2	25,1	**Z**	**m**
(E/B-1)/Cv	-0,18	-0,12	-0,10	-0,20	0,00	0,04	-0,13	-0,20	0,08	**-0,09**	**0,04**

In addition, Canephron® N potentiates increasing urina P/Ca Ratio as marker of Parathyrine Activity, serum level IgG and Bactericidic Capacity of Neutrophiles vs Staphylococcus aureus as well as decreasing Urea and Creatinine plasma level, Sodium urina concentration and Neutrophiles Phagocytose Count vs Escherichia coli (Table 6). We interpret this immunomodulation as neurogenic endocrine and metabolic caused and beneficial for prevention of recurrence of inflammation in the kidney and gall-bladder.

Table 6. The parameters increase or decrease which influenced the standard balneotherapy Canephron® N increases

Gr-ps/Par-s	F3-β, %	PTA= $(P/Ca)^{0,5}$	IgG, g/l	BCN vs St. aur., 10^9/l			$Urea_P$, mM/l	$Creatinine_P$, μM/l	CNa_U, mM/l	Microb. Count vs E. coli		
Before	20,7	2,00	12,6	92,3			7,09	100,7	119,7	64,4		
Cv	0,388	0,246	0,282	0,301			0,177	0,127	0,330	0,089		
Control	26,9	2,37	14,3	104,3	**Z**	**m**	6,21	88,73	101,0	60,0	**Z**	**m**
(C/B-1)/Cv	0,78	0,74	0,49	0,43	**0,61**	**0,09**	-0,71	-0,93	-0,47	-0,77	**-0,72**	**0,10**
Experiment	31,0	2,56	15,8	115,8	**Z**	**m**	5,73	85,53	90,0	57,7	**Z**	**m**
(E/B-1)/Cv	1,30	1,13	0,90	0,84	**1,04**	**0,10**	-1,09	-1,18	-0,75	-1,18	**-1,05**	**0,10**

Finally, a number of parameters of Urina, Cholekinetics, Immunity, EEG and HRV not subordinated to the influence of the tested drug (Table 7).

Table 7. Options to increase or decrease which influenced standard balneotherapy Canephron® N has no effect

Gr-ps/Par-s	Fr. α, Hz	CTA= $(Ca•P)^{-0,5}$	Kill. St. aur., %			GF, ml/m	Diur, l/day	CP_U, mM/l	EP_U, mM/d	UreaE mM/d	Kill. E. coli, %	Eos. %		
Before	10,3	10,4	46,7			96	2,19	9,4	20,5	682	44,6	2,5		
Cv	0,073	0,261	0,126			0,297	0,212	0,230	0,289	0,260	0,160	0,528		
Control	10,8	17,2	58,6	**Z**	**m**	112	2,69	15,3	40,8	783	53,3	3,2	**Z**	**m**
(C/B-1)/Cv	0,76	2,49	2,03	**1,76**	**0,52**	0,56	1,07	2,74	3,43	0,57	1,21	0,52	**1,44**	**0,44**
Experiment	10,6	16,0	56,7	**Z**	**m**	110	2,71	15,0	40,5	769	51,6	3,2	**Z**	**m**
(E/B-1)/Cv	0,41	2,07	1,71	**1,39**	**0,50**	0,51	1,11	2,62	3,37	0,50	0,97	0,47	**1,36**	**0,44**

Extension of Table 7

Gr-ps/Par-s	Fp1-α, %	LF/HF HRV	IC HRV	Lympho-cytes, %	V_0, ml	V_5, ml	V_{15}, ml	V_{30}, ml	V_5, %	V_{15}, %	V_{30}, %		
Before	41,3	4,16	8,75	37,2	48,9	47,8	40,43	35,1	97,5	81,3	69,7		
Cv	0,366	1,110	0,960	0,175	0,307	0,317	0,378	0,418	0,019	0,098	0,135		
Control	31,0	2,70	4,87	33,4	41,38	39,47	30,50	22,68	95,24	73,45	54,36	**Z**	**m**
(C/B-1)/Cv	-0,68	-0,32	-0,46	-0,58	-0,50	-0,55	-0,65	-0,85	-1,22	-0,99	-1,63	**-0,77**	**0,12**
Experiment	34,0	2,00	4,79	34,6	41,70	39,90	31,37	22,17	95,47	74,46	52,53	**Z**	**m**
(E/B-1)/Cv	-0,48	-0,47	-0,47	-0,40	-0,48	-0,52	-0,59	-0,88	-1,10	-0,87	-1,83	**-0,74**	**0,13**

The procedure discriminant analysis (method forward stepwise) reveals among registered settings those for aggregate which patients before treatment and after treatment in two ways significantly different

among themselves. Identification turned out 23 parameters, including 9 **neural**, 6 **immune**, 4 **urinary**, 2 **cholekinetic** and 2 **metabolic** (Table 8)**.**

Information about these options condensed in two canonical discriminant roots (76% in Root 1 and 24% in Root 2). This reflects the major radical 7 parameters **inverse** way while other 7 variables **directly**. On the other hand, minor root **inversely** correlated with 7 parameters and **directly** with only two (Table 9).

Table 8. Discriminant Function Analysis Summary. Wilks' Lambda: 0,014; approx. $F_{(46)}$=6,98; $p<10^{-6}$

Variables currently in model	Wilks'Λ	Part. Λ	F-rem	p	Toler	F ent	p	Λ	F	p
Gall-bladder PPV_{30}, %	,023	,635	6,31	,0068	,191	14,2	10^{-4}	,607	14,2	10^{-5}
Phosphaturia, mM/l	,017	,858	1,82	,1852	,501	9,12	10^{-3}	,426	11,4	10^{-6}
Diurese, l/24 h	,032	,454	13,2	,0002	,269	3,68	,034	,363	9,24	10^{-6}
Killing Index vs Staph. aureus, %	,021	,701	4,70	,0200	,322	6,73	,003	,273	9,36	10^{-6}
Uricemia, mM/l	,017	,855	1,87	,1778	,326	3,31	,047	,234	8,52	10^{-6}
Gall-bladder PPV_{15}, ml	,017	,843	2,05	,1531	,211	3,05	,059	,203	7,94	10^{-6}
Frequency θ-Rhythm, Hz	,019	,774	3,21	,0599	,323	2,39	,105	,180	7,37	10^{-6}
LF/HF HRV	,022	,649	5,95	,0086	,035	3,04	,060	,155	7,14	10^{-6}
Microbial Count vs Staph. aureus	,025	,590	7,64	,0030	,148	3,31	,048	,131	7,07	10^{-6}
Chloriduria, mM/l	,030	,479	12,0	,0003	,382	2,85	,071	,112	6,95	10^{-6}
Activity Regulatory Systems Index	,023	,626	6,58	,0057	,321	1,77	,185	,102	6,60	10^{-6}
Theophilinesensitive T-Lymph., %	,021	,705	4,60	,0214	,441	1,68	,202	,092	6,30	10^{-6}
PS VLF HRV, %	,026	,562	8,57	,0018	,095	2,16	,131	,081	6,17	10^{-6}
(VLF+LF)/HF HRV	,020	,725	4,17	,0291	,030	1,98	,155	,072	6,03	10^{-6}
PS ULF HRV, %	,031	,472	12,3	,0003	,262	1,90	,167	,064	5,91	10^{-6}
Microbial Count vs E. coli	,025	,585	7,80	,0028	,122	2,58	,093	,054	5,96	10^{-6}
PSD F8-β, %	,029	,496	11,2	,0005	,125	2,96	,068	,045	6,13	10^{-6}
PSD F3-β, %	,025	,574	8,17	,0022	,105	5,31	,011	,032	6,86	10^{-6}
PSD C4-δ, %	,021	,681	5,15	,0146	,278	4,16	,027	,024	7,39	10^{-6}
Glomerular Filtration, ml/min	,017	,835	2,18	,1370	,264	2,25	,126	,021	7,45	10^{-6}
Bacterocidity vs Staph. aur., 10^9/l	,016	,883	1,46	,2548	,304	1,72	,201	,018	7,36	10^{-6}
Serum IgG, g/l	,017	,860	1,79	,1906	,407	1,48	,249	,016	7,22	10^{-6}
Creatininemia, μM/l	,016	,907	1,13	,3404	,418	1,13	,340	,015	6,98	10^{-6}

Table 9. Factor Structure Matrix. Correlations Variables-Canonical Roots (Pooled-within-groups correlations) and Means of Canonical Variables

Variables currently in model	Root 1	Root 2	Basal level	Control group	Experimen-tal group
Gall-bladder PPV_{30}, %	**-0,22**	,04	69,7	54,4	52,5
Creatininemia, μM/l	**-0,15**	,02	101	89	85
Microbial Count vs E. coli	**-0,10**	,00	64,4	60,0	57,7
Gall-bladder PPV_{15}, ml	**-0,08**	,04	40,4	30,5	31,4
(VLF+LF)/HF HRV	**-0,07**	,04	8,8	4,9	4,8
LF/HF HRV	**-0,06**	,01	4,2	2,7	2,0
Microbial Count vs Staph. aureus	**-0,04**	,05	64,0	59,2	61,4
Diurese, l/24 h	**0,19**	-,10	2,19	2,69	2,71
Phosphaturia, mM/l	**0,17**	-,10	9,4	15,3	15,0
Killing Index vs Staph. aureus, %	**0,17**	-,09	46,7	58,6	56,7
Serum IgG, g/l	**0,11**	,02	12,6	14,3	15,8
Bacterocidity vs Staph. aur., 10^9/l	**0,07**	,02	92	104	116
PSD F3-β, %	**0,07**	-,01	20,7	26,9	31,0
Glomerular Filtration, ml/min	**0,05**	-,02	96	112	110
Uricemia, mM/l	-,01	**-0,19**	0,32	0,38	0,30

Theophilinesensitive T-Lymph., %	-,05	**-0,17**	23,5	25,6	20,4
Chloriduria, mM/l	-,06	**-0,13**	103	109	81
Activity Regulatory Systems Index	-,03	**-0,12**	3,9	4,9	2,8
PS ULF HRV, %	,03	**-0,10**	2,0	4,4	2,2
PSD C4-δ, %	,00	**-0,07**	18,7	23,2	16,7
PSD F8-β, %	,02	**-0,07**	30,6	39,2	31,4
PS VLF HRV, %	-,01	**0,10**	41,2	31,4	42,1
Frequency θ-Rhythm, Hz	,02	**0,06**	6,5	6,3	6,9
		Roots	**Means of Canonical Variables**		
		1	-3,4	+1,7	+4,7
		2	+0,6	-3,2	+2,0

Table 10. Coefficients and Constants for Canonical Variables as well as Squared Mahalanobis Distances between Groups

Coefficients for Canonical Variables	Standardized		Raw	
Variables currently in model	Root 1	Root 2	Root 1	Root 2
Gall-bladder PPV_{30}, %	-1,431	-,125	-,207	-,018
Phosphaturia, mM/l	,110	-,583	,025	-,134
Diurese, l/24 h	,900	-1,264	2,375	-3,334
Killing Index vs Staph. aureus, %	,964	,294	,171	,052
Uricemia, mM/l	,440	-,578	5,830	-7,656
Gall-bladder PPV_{15}, ml	,890	,111	,086	,011
Frequency θ-Rhythm, Hz	,392	,834	,376	,801
LF/HF HRV	-3,168	1,015	-,993	,318
Microbial Count vs Staph. aureus	1,146	1,390	,151	,183
Chloriduria, mM/l	-,768	-1,011	-,023	-,030
Activity Regulatory Systems Index	-,291	-1,165	-,141	-,563
Theophilinesensitive T-Lymph., %	-,553	-,695	-,115	-,144
PS VLF HRV, %	-2,232	,131	-,152	,009
(VLF+LF)/HF HRV	3,153	-,153	,535	-,026
PS ULF HRV, %	-1,067	-1,094	-,337	-,346
Microbial Count vs E. coli	-1,510	-1,274	-,205	-,173
PSD F8-β, %	-1,196	-1,839	-,071	-,109
PSD F3-β, %	1,690	1,321	,144	,112
PSD C4-δ, %	1,096	-,203	,087	-,016
Glomerular Filtration, ml/min	-,653	,538	-,026	,022
Bacterocidity vs Staph. aur., 10^9/l	,357	-,576	,013	-,021
Serum IgG, g/l	,509	,360	,155	,110
Creatininemia, μM/l	-,427	-,260	-,042	-,026
Squared Mahalanobis Distances	**Constants**		5,567	14,47
B-C: 43 ($F=6,8$; $p<10^{-4}$);	**Eigenvalues**		12,73	4,02
B-E: 71 ($F=11,4$; $p<10^{-6}$);	**Discr. Properties**		76 %	24 %
C-E: 38 ($F=4,6$; $p<10^{-3}$)	**Canonical R**		0,963	0,895

Calculation according to Table 10 values personal roots allows to visualize the location of each patient (Fig. 3) as well as their groups (Fig. 4) in the two-dimensional information space.

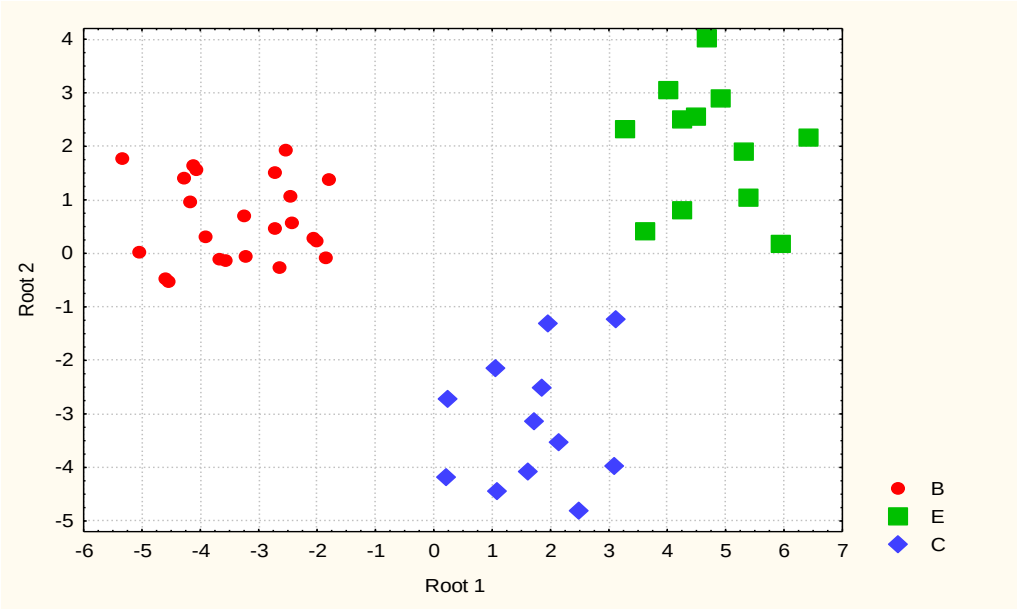

Fig. 3. Personal unstandardized canonical scores before (B) and after therapy in control (C) and experimental (E) groups

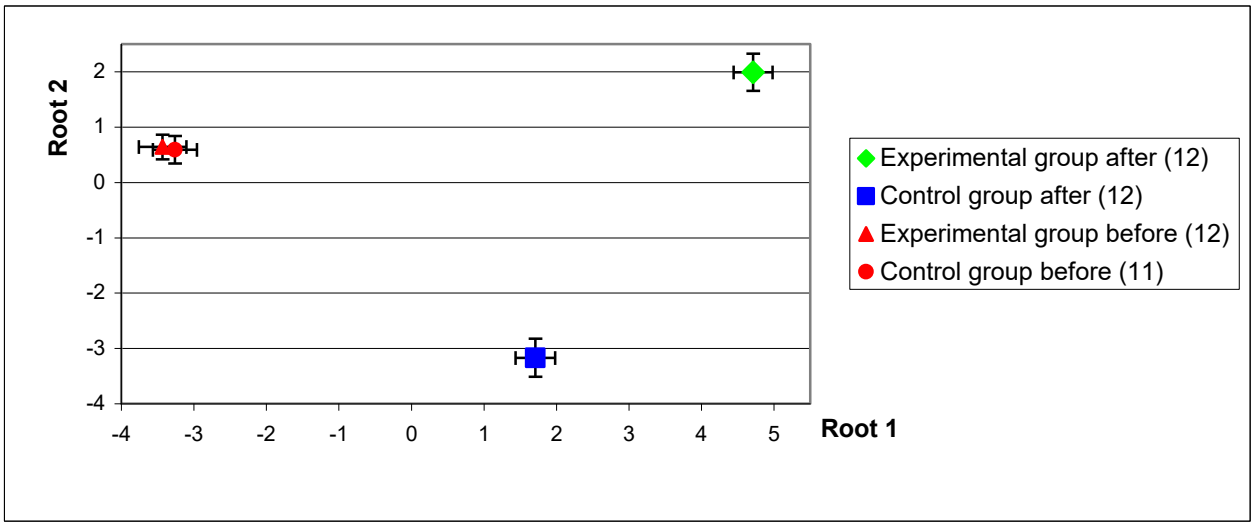

Fig. 4. Means unstandardized canonical scores before and after therapy in control and experimental groups

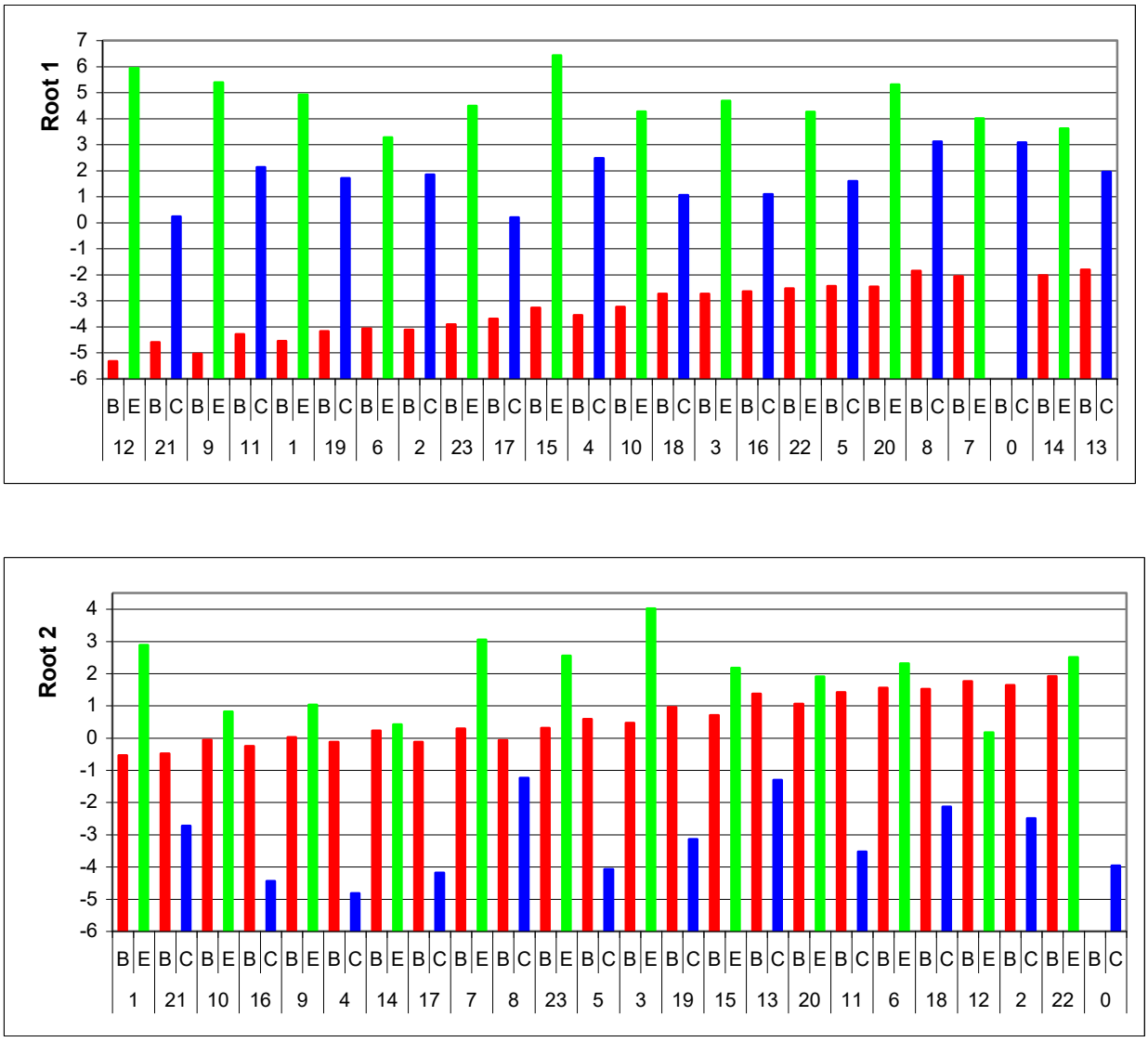

Fig. 5. Personal unstandardized canonical scores for Root 1 and 2 before (B) and after therapy in control (C) and experimental (E) groups

Delimitiation along the axis of the first root reflect the **decrease** or **increase** the 14 initial parameters of patients after standard balneotherapy and potentiation of changes additional drug use.

On the other hand, the overlap zones of initial state and after combined treatment along the axis of the second root displays the prevention or reversing by Canephron® N change the initial settings predefined standard balneotherapy.

Personal effects standard and combined therapy for neuroendocrine-immune complex and metabolism visualized in Fig. 5.

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