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Sexual dimorphism in relationships between of plasma creatinine and some neuro-endocrine parameters

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Summary

Background. Earlier we found that plasma uric acid and urea causes modulating effects on neuro-endocrine parameters, as well as reactive anxiety, but these effects are significantly different in men and women of different ages. The **purpose** of this study is to analyze the relationships between the plasma creatinine level and some psycho-neuro-endocrine parameters in the same cohort. **Materials and Methods.** The object of observation were almost healthy volunteers: 31 males (24÷69 y) and 30 females, from among them 18 postmenopausal (48÷76 y) and 12 of reproductive age (30÷45 y). In basal conditions we determined plasma levels of creatinine and adaptation hormones, estimated the severity of the trait and reactive anxiety, recorded the ongoing HRV and EEG. After 4 or 7 days, repeated testing was performed. **Results.** By building regression models with stepwise exclusion, it was found that in men plasma creatinine downregulates the level of Cortisol ($r=-0,41$) while upregulates the levels of Testosterone ($r=0,36$) and Calcitonin ($r=0,30$). The degree of determination of endocrine parameters is 31,9%. In postmenopausal women, creatinine also upregulates Testosterone ($r=0,43$) while downregulates the amplitude and PSD of β -rhythm in different loci as well as causes right lateralization of β -rhythm. The degree of determination of neuro-endocrine parameters is 61,2%. In women of reproductive age creatinine upregulates the PSD of ULF band HRV and α -rhythm in 5 loci as well as the Entropy of EEG in F3 locus while downregulates the Entropy in T6 locus, F3- δ and T6- θ PSD as well as Cortisol level. The degree of determination of neuro-endocrine parameters is 94,0%. **Conclusion.** Plasma creatinine has a modulating effect on neuro-endocrine parameters, but this effect is significantly different in men and women of different ages.

Keywords: plasma creatinine, cortisol, testosterone, aldosterone, triiodothyronine, calcitonin, ongoing EEG, HRV, anxiety, men, women.

INTRODUCTION

Earlier we found that plasma **uric acid** and **urea** causes modulating effects on neuro-endocrine parameters, as well as reactive anxiety, but these effects are significantly different in men and women of different ages [4-7,14].

The **purpose** of this study is to analyze the relationships between the plasma **creatinine** level and some psycho-neuro-endocrine parameters in the same cohort.

MATERIAL AND METHODS

The object of observation were employees of the clinical sanatorium "Moldova" and PrJSC "Truskavets' Spa": 31 males (24÷69 y) and 30 females, from among them 18 postmenopausal (48÷76 y) and 12 of reproductive age (30÷45 y). The volunteers were considered practically healthy (without a clinical diagnosis), but the initial testing revealed deviations from the norm in a number of parameters of the neuro-endocrine-immune complex as a manifestation of maladaptation [4,6].

Testing was performed twice with an interval of 4 (in 11 men and 10 women; "Moldova") or 7 (in 10 men and 10 women; "Truskavets' Spa") days.

We determined the plasma levels of the Creatinine (by Jaffe's color reaction by Popper's method) [8] as well as main adaptation hormones Cortisol, Aldosterone, Testosterone, Triiodothyronine and Calcitonin (by the ELISA with the use of corresponding sets of reagents from "Алкор Био", XEMA Co. Ltd, and DRG International Inc).

The analyzers "Pointe-180" ("Scientific", USA), "Reflotron" (Boehringer Mannheim, BRD) and "RT-2100C" (PRCh) were used.

The levels of the trait and reactive anxiety estimated by STAI of Spielberger ChD [18] in modification of Khanin YL [13].

The state of the autonomic and central nervous systems was evaluated according to the parameters of heart rate variability [2,3,11,17] (software-hardware complex "CardioLab+HRV", KhAI-MEDICA, Kharkiv) and QEEG (hardware-software complex "NeuroCom Standard", KhAI MEDICA, Kharkiv).

In addition to routine parameters, Shannon's CE [16] Entropy of HRV and EEG were calculated [10,15]. See the previous articles for details [5,14].

Results processed by using the software package "Statistica 6.4".

RESULTS AND DISCUSSION

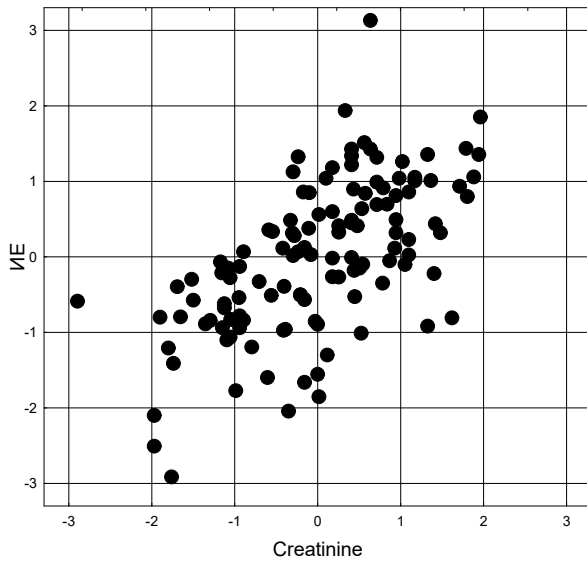
At the first stage regression models were built by step-by-step exclusion of the variable until the maximum value of Adjusted R^2 was reached.

For the cohort as a whole, the regression model includes two hormones out of 4 registered, only one HRV parameter and 7 EEG parameters in the absence of anxiety parameters. The degree of determination of neuro-endocrine parameters by plasma creatinine level was moderate (Table 1 and Fig. 1).

Table 1. Regression Summary for Creatinine plasma in total cohort

$R=0,613$; $R^2=0,376$; Adjusted $R^2=0,320$; $F_{(10)}=6,7$; $p<10^{-5}$

N=122		Beta	St. Err. of Beta	B	SE of B	$t_{(111)}$	p-level
Variables	r		Intercept	94,68	5,00	18,9	10^{-6}
Testosterone, nM/L	0,40	0,340	0,078	0,640	0,147	4,36	10^{-4}
ULF HRV PSD, msec²	0,22	0,209	0,077	0,0048	0,0018	2,73	0,007
Cortisol, nM/L	-0,30	-0,227	0,077	-0,026	0,009	-2,93	0,004
T5-θ PSD, %	-0,26	-0,153	0,094	-0,445	0,273	-1,63	0,106
Fp1-θ PSD, %	-0,24	-0,144	0,107	-0,360	0,268	-1,35	0,181
Fp2-θ PSD, %	-0,19	-0,139	0,109	-0,366	0,288	-1,27	0,206
C4-θ PSD, %	-0,18	0,155	0,115	0,480	0,355	1,35	0,178
C3-β PSD, μV²/Hz	-0,23	-0,185	0,083	-0,0324	0,0144	-2,23	0,028
F7-β PSD, %	-0,16	-0,197	0,093	-0,168	0,079	-2,12	0,036
Entropy F7	-0,17	0,135	0,102	8,162	6,192	1,32	0,190



$R=0,613$; $R^2=0,376$; $\chi^2_{(10)}=54$; $p<10^{-6}$; $\Lambda \text{ Prime}=0,624$

Fig. 1. Scatterplot of canonical correlation between Creatinine plasma (X-line) and Neuroendocrine parameters (Y-line)

Linkage analysis in men alone also revealed a downregulation of cortisol (Fig. 2) and upregulation of testosterone (Fig. 3) as well as calcitonin (Fig. 4).

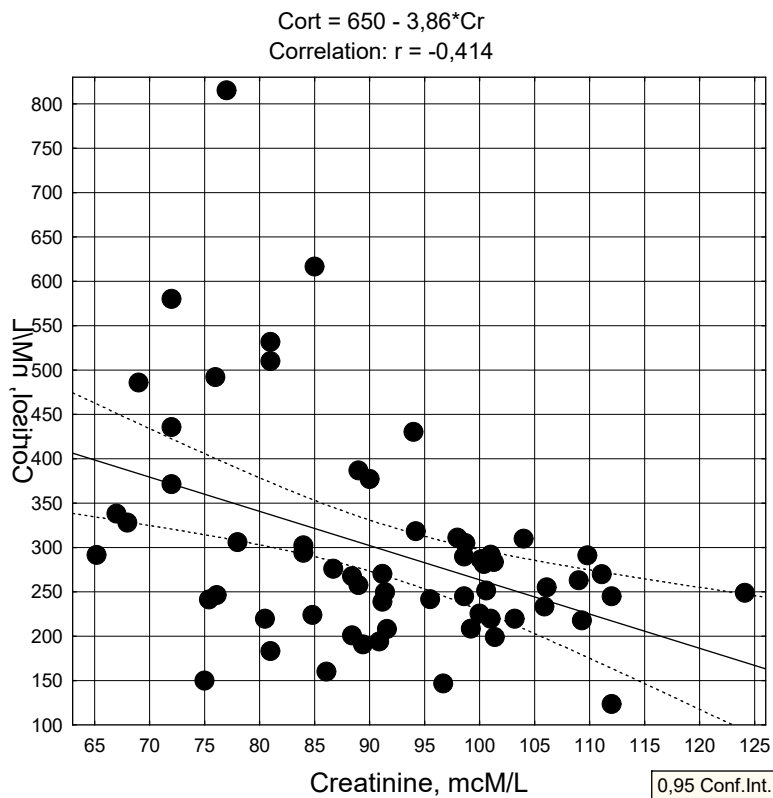


Fig. 2. Scatterplot of correlation between Creatinine (X-line) and Cortisol (Y-line) plasma at Men

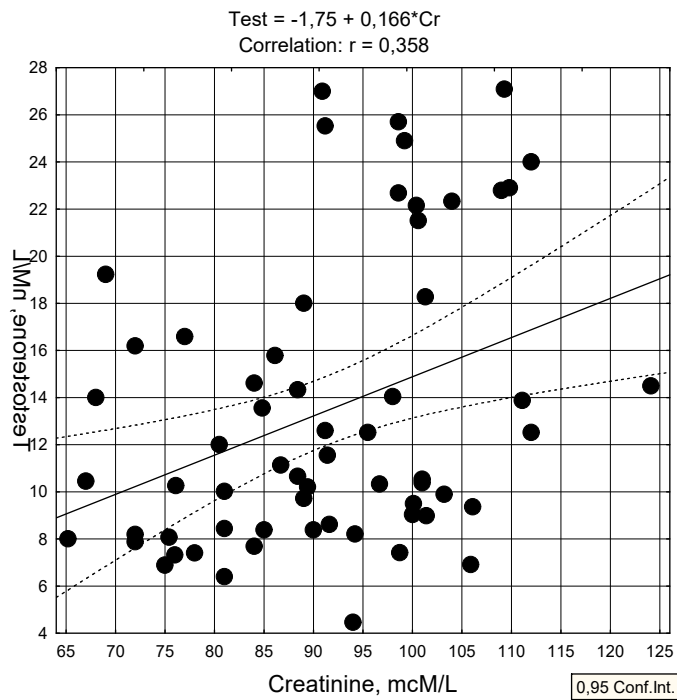


Fig. 3. Scatterplot of correlation between Creatinine (X-line) and Testosterone (Y-line) plasma at Men

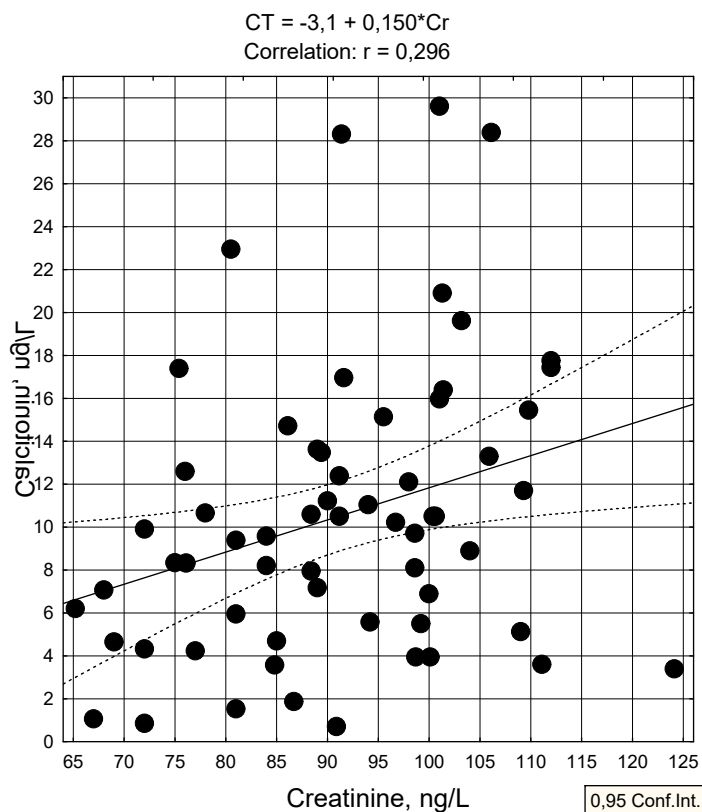


Fig. 4. Scatterplot of correlation between Creatinine (X-line) and Calcitonin (Y-line) plasma at Men

In addition, a negative correlation of creatinine with relative PSD of VLF band HRV was found (Fig. 5), which, in turn, is positively correlated with the level of cortisol (Fig. 6).

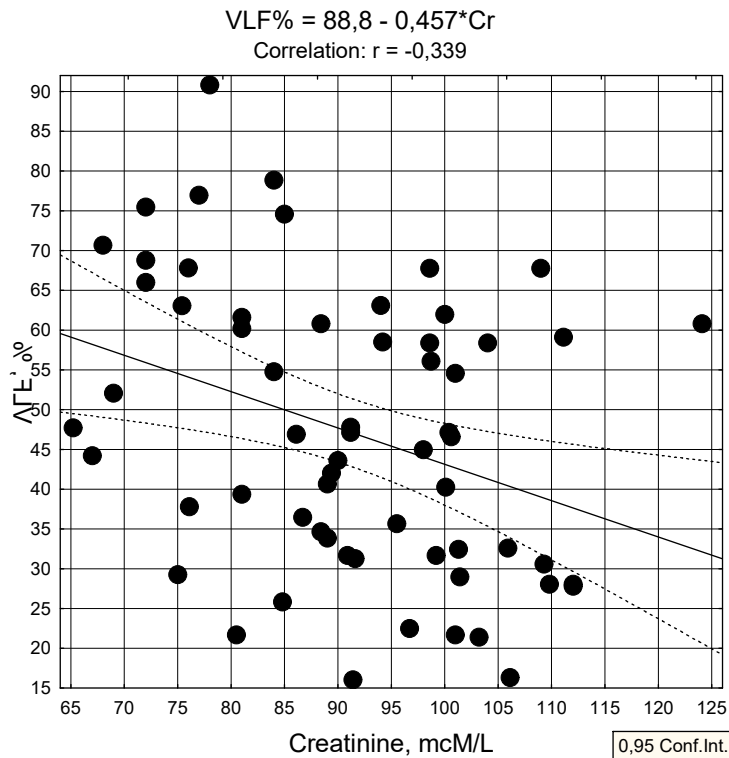


Fig. 5. Scatterplot of correlation between Creatinine plasma (X-line) and PSD of VLF band HRV (Y-line) at Men

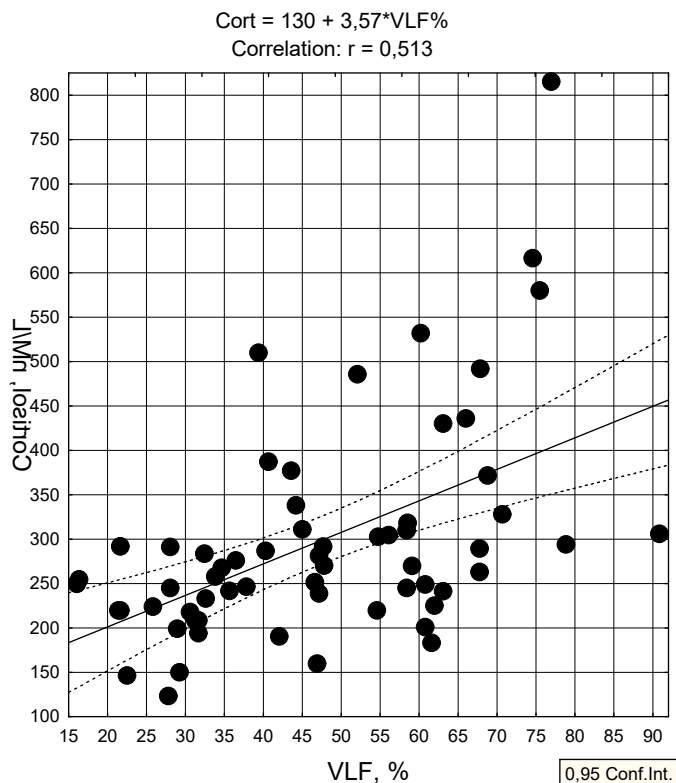


Fig. 6. Scatterplot of correlation between PSD of VLF band HRV (X-line) and Cortisol plasma (Y-line) at Men

There are opinions that VLF band (0,040±0,003 Hz) directly reflects both vagal and sympathetic tone [1] or vagal tone only [19] as well as saliva testosterone level [20] while inversely - renin-angiotensin-aldosterone system activity [1,20]. It was reported that low VLF power has been correlated with low levels of testosterone,

while other biochemical markers, such as those mediated by the hypothalamic–pituitary–adrenal axis (e.g., cortisol), have not [20].

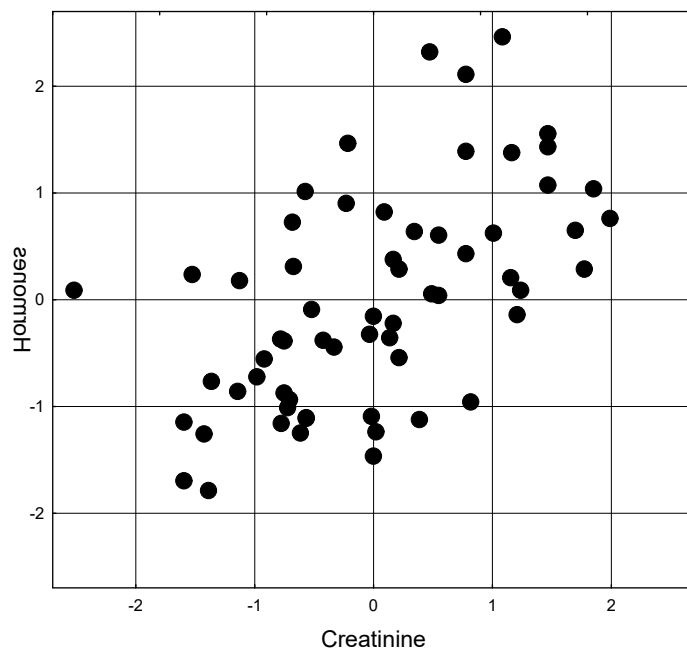
However, in the cohort of men observed by us, the relationship of relative PSD of VLF band with testosterone turned out to be close to zero, while with cortisol it was moderately positive, which is inconsistent with the data of the cited authors. In the end, the VLF band turned out to be outside the regression model for some reason.

The degree of determination of endocrine parameters by creatinine is 31,9% (Table 2 and Fig. 7).

Table 2. Regression Summary for Creatinine plasma in Men

R=0,564; R²=0,319; Adjusted R²=0,283; F_(3,6)=9,0; p<10⁻⁴

N=62		Beta	St. Err. of Beta	B	SE of B	t ₍₅₈₎	p-level
Variables	r		Intercept	87,0	6,3	13,8	10 ⁻⁶
Cortisol, nM/L	-0,41	-0,319	0,114	-0,034	0,012	-2,80	0,007
Testosterone, nM/L	0,36	0,338	0,109	0,727	0,235	3,09	0,003
Calcitonin, ng/L	0,30	0,221	0,113	0,437	0,225	1,95	0,057



R=0,564; R²=0,319; $\chi^2_{(3)}=22$; p<10⁻⁴; Λ Prime=0,681

Fig. 7. Scatterplot of canonical correlation between Creatinine plasma (X-line) and Endocrine parameters (Y-line) at Men

In postmenopausal women, creatinine also upregulates Testosterone (Fig. 8) while downregulates the amplitude and PSD of β -rhythm in three left loci as well as causes right lateralization of β -rhythm (Fig. 9). The degree of determination of neuro-endocrine parameters is 61,2% (Table 3 and Fig. 10).

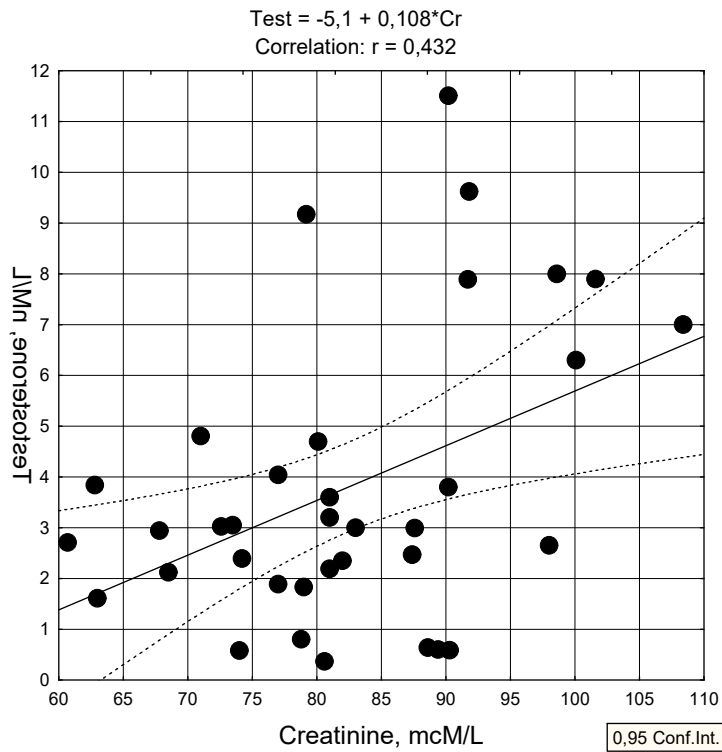


Fig. 8. Scatterplot of correlation between Creatinine (X-line) and Testosterone (Y-line) plasma at postmenopausal Women

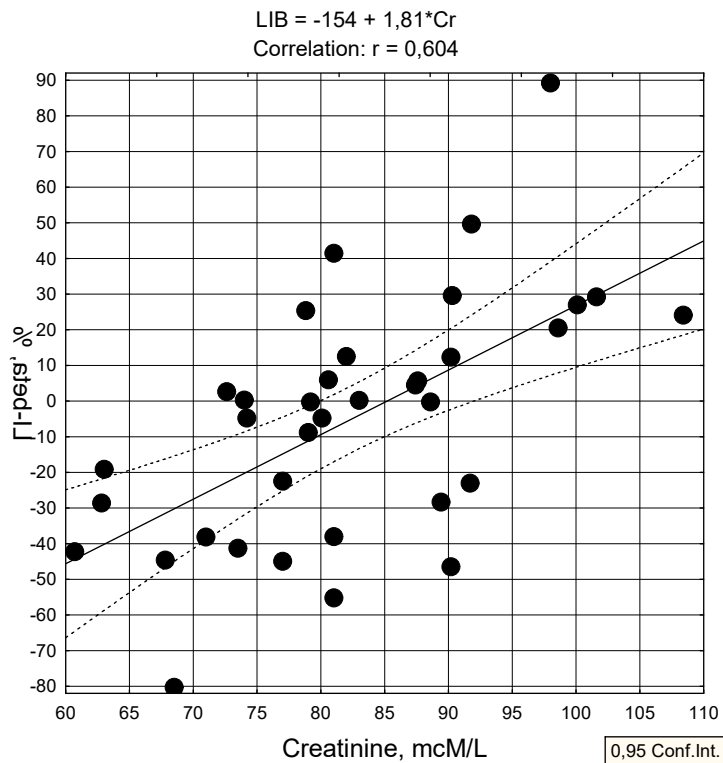
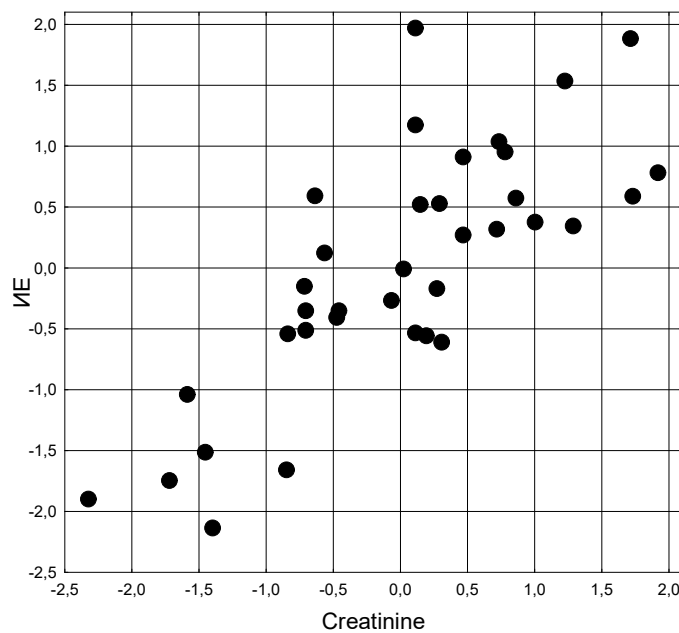


Fig. 9. Scatterplot of correlation between Creatinine plasma (X-line) and Laterality of beta-rhythm (Y-line) at postmenopausal Women

Table 3. Regression Summary for Creatinine plasma in postmenopausal (48÷76 y) Women
 $R=0,782$; $R^2=0,612$; Adjusted $R^2=0,515$; $F_{(7,3)}=6,3$; $p=0,0002$

N=36		Beta	St. Err. of Beta	B	SE of B	$t_{(28)}$	p-level
Variables	r		Intercept	81,1	7,0	11,5	10^{-6}
Testosterone, nM/L	0,43	0,537	0,143	2,153	0,574	3,75	0,001
Laterality β , %	0,60	0,715	0,147	0,239	0,049	4,87	10^{-4}
Amplitude β , μV	-0,34	-0,337	0,300	-0,822	0,734	-1,12	0,272
T3- β PSD, $\mu V^2/Hz$	-0,37	0,473	0,254	0,047	0,025	1,86	0,073
F3- β PSD, $\mu V^2/Hz$	-0,33	-0,348	0,249	-0,054	0,038	-1,40	0,174
P3- β PSD, $\mu V^2/Hz$	-0,29	0,660	0,265	0,069	0,028	2,49	0,019
T3- θ PSD, $\mu V^2/Hz$	-0,26	-0,314	0,148	-0,049	0,023	-2,12	0,043



$R=0,782$; $R^2=0,612$; $\chi^2_{(7)}=29$; $p=0,0002$; Λ Prime=0,388

Fig. 10. Scatterplot of canonical correlation between Creatinine plasma (X-line) and Neuro-endocrine parameters at postmenopausal Women (Y-line)

In women of reproductive age creatinine upregulates the PSD of ULF band HRV and α -rhythm in 5 loci (Table 4 and Fig. 11) and T6- β PSD while downregulates the PSD of θ -rhythm in T6 (Fig. 12) and P4 (Fig. 13) loci and F3- δ PSD. In addition, a positive correlation with the trait anxiety (Fig. 14) and the Entropy of EEG in F3 locus while negative correlation with the Entropy in T6 locus and Cortisol level (Table 4) was found. It is interesting that two parameters were outside the regression model.

The physiological essence of the ULF band remains a subject of debate. It is speculated that ULF band (0,015÷0,003 Hz) associated with oscillation blood level of norepinephrine (0,002 Hz) and 17-OKS (0,0019 Hz) [12]. The latter assumption is inconsistent with our data on the lack of correlation between PSD of ULF band and Cortisol level ($r=-0,07$).

The degree of determination of neuro-endocrine parameters by creatinine is 94,0% (Table 4 and Fig. 15).

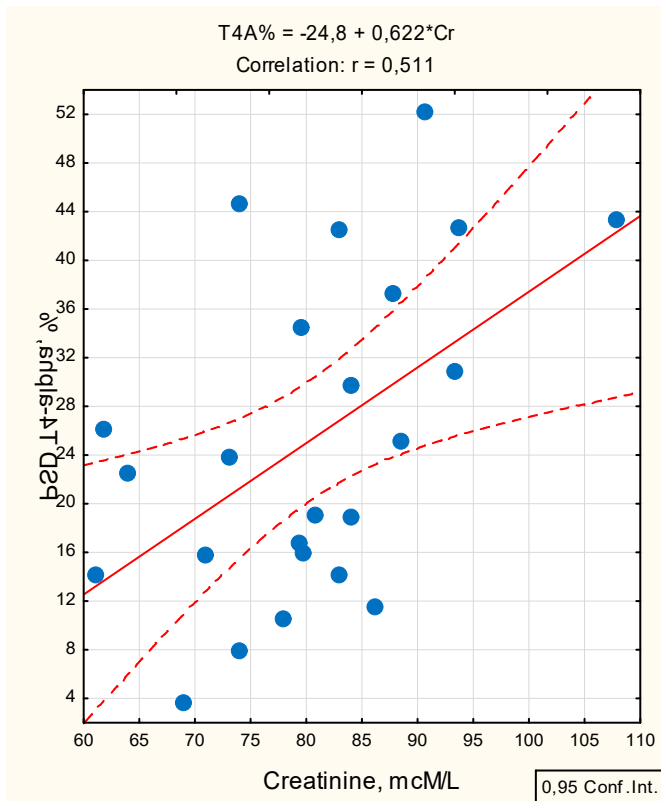


Fig. 11. Scatterplot of correlation between Creatinine plasma (X-line) and PSD of alpha-rhythm in T4 locus (Y-line) at premenopausal Women

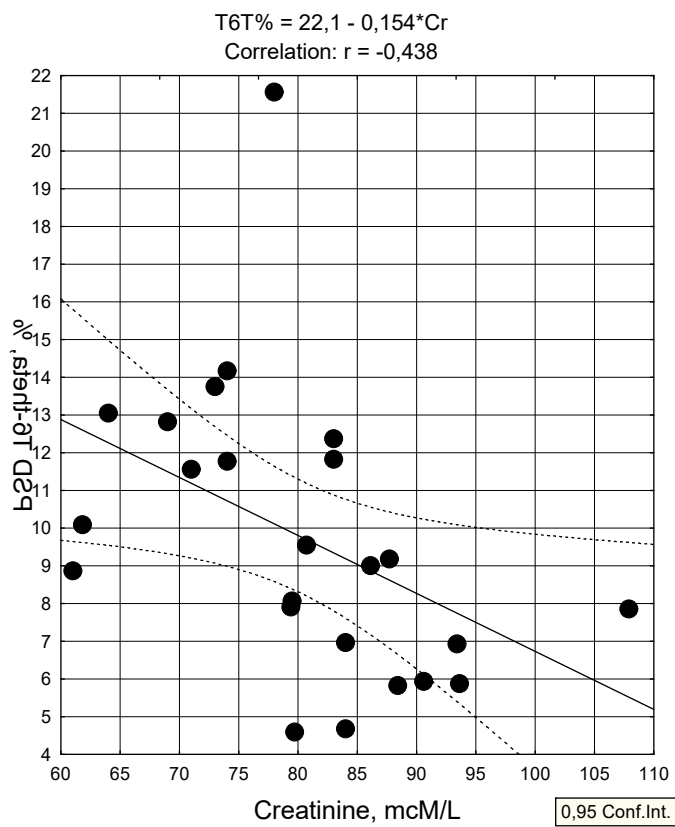


Fig. 12. Scatterplot of correlation between Creatinine plasma (X-line) and PSD of theta-rhythm in T6 locus (Y-line) at premenopausal Women

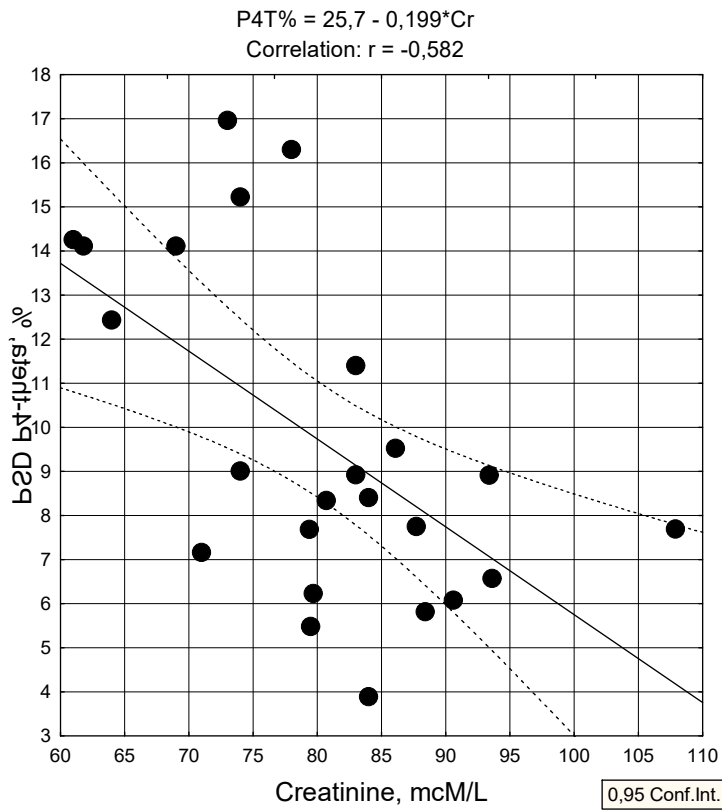


Fig. 13. Scatterplot of correlation between Creatinine plasma (X-line) and PSD of theta-rhythm in T6 locus (Y-line) at premenopausal Women

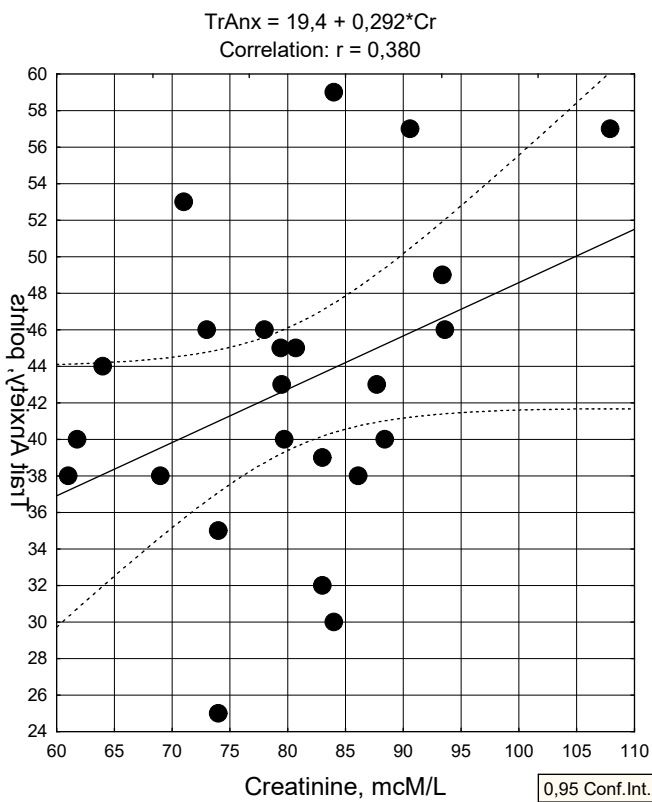
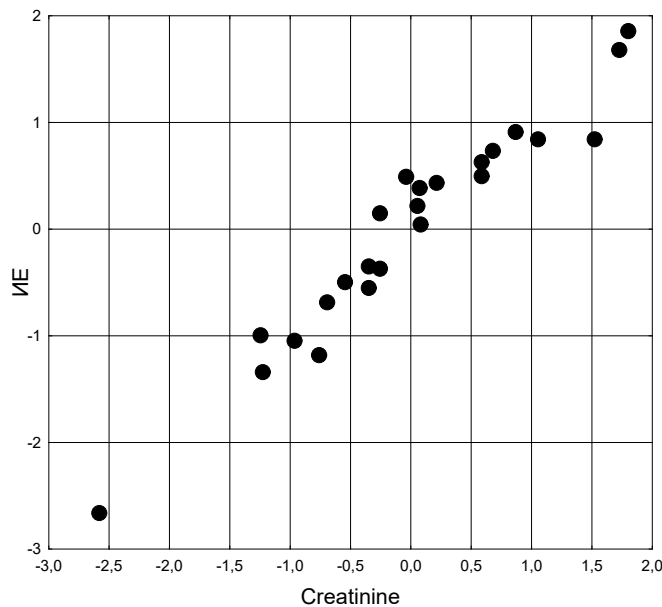


Fig. 14. Scatterplot of correlation between Creatinine plasma (X-line) and Trait Anxiety (Y-line) at premenopausal Women

Table 4. Regression Summary for Creatinine plasma in premenopausal (30÷45 y) Women
 $R=0,969$; $R^2=0,940$; Adjusted $R^2=0,874$; $F_{(12,1)}=14,3$; $p=0,00005$

N=24		Beta	St. Err. of Beta	B	SE of B	$t_{(11)}$	p-level
Variables	r		Intercept	128,9	13,7	9,42	10^{-6}
ULF HRV PSD, msec²	0,51	0,616	0,098	0,0108	0,0017	6,27	10^{-4}
T4-α PSD, %	0,51	-0,643	0,205	-0,528	0,169	-3,13	0,009
Entropy F3	0,48	0,523	0,138	36,26	9,542	3,80	0,003
F3-α PSD, %	0,42	0,567	0,187	0,424	0,140	3,04	0,011
T6-α PSD, $\mu V^2/Hz$	0,42	-0,190	0,175	-0,0134	0,0123	-1,09	0,300
C4-α PSD, %	0,41	-0,421	0,284	-0,316	0,213	-1,48	0,166
P4-α PSD, %	0,39	0,544	0,296	0,347	0,189	1,84	0,093
T6-β PSD, $\mu V^2/Hz$	0,43	0,689	0,114	0,1621	0,0268	6,04	0,0001
T6-θ PSD, %	-0,44	0,395	0,172	1,124	0,489	2,30	0,042
Entropy T6	-0,43	-0,881	0,161	-112,5	20,53	-5,48	0,0002
F3-δ PSD, %	-0,40	0,729	0,179	0,343	0,084	4,08	0,002
Cortisol, nM/L	-0,38	-0,801	0,184	-0,068	0,016	-4,36	0,001



$R=0,969$; $R^2=0,940$; $\chi^2_{(12)}=45$; $p=0,00005$; Λ Prime=0,060

Fig. 15. Scatterplot of canonical correlation between Creatinine plasma (X-line) and Neuro-endocrine parameters at premenopausal Women (Y-line)

In order to visualize the strength and directionality of the relationships between plasma creatinine levels and neuro-endocrine parameters at premenopausal and postmenopausal women as well as men, three profiles were created (Fig. 16).

Next, the parameters were grouped into clusters (Fig. 17).

As in the case of urea [7], it seems that the differences between the neuro-endocrine effects of creatinine in the three groups of people are related to the levels of sex hormones, but cannot be completely reduced to them. This will be the subject of a separate study.

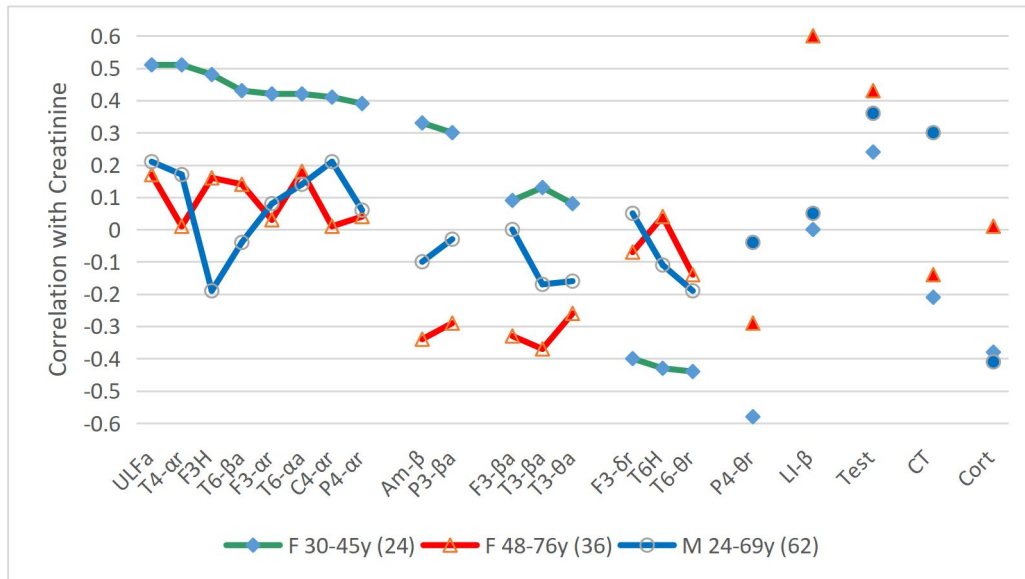


Fig. 16. Profiles of relationships between plasma Creatinine and Neuro-Endocrine parameters at premenopausal and postmenopausal Females as well as Males

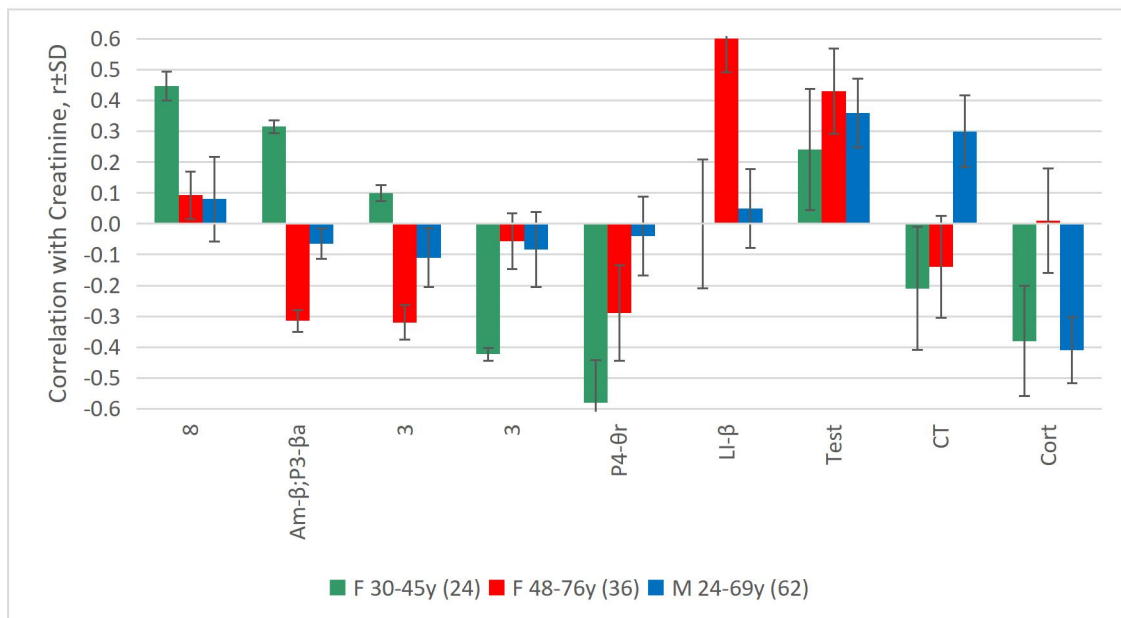


Fig. 17. Clusters of relationships between plasma Creatinine and Neuro-Endocrine parameters at premenopausal and postmenopausal Females as well as Males. The number of variables in the cluster is given

ACKNOWLEDGMENT

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ACCORDANCE TO ETHICS STANDARDS

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

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