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Neuro-endocrine correlates and predictors of electrokinetic index changes in buccal epithelium during rehabilitation treatment: a multivariate analysis

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Abstract. ***Background.*** *Earlier we showed that qualitative-quantitative clusters of blood pressure (BP) are very clearly different from each other by age, sex and the constellation of neuro-endocrine, immune and metabolic variables, which we called the tensioregulome. The tensioregulome also included the electrokinetic index (EKI) of the buccal epithelium, which cannot formally be attributed to either neuro-endocrine-immune or metabolic constellations. The aim of the study is to determine how changes in EKI levels correlate with changes in brain electrical activity, heart rate variability (HRV) and adaptation hormones levels in individuals with maladaptation.* ***Materials and methods.*** *Under observation, there were 42 men (49 ± 15 years old) and 30 women (51 ± 13 years old) without clinical diagnosis or with chronic pyelonephritis in the phase of remission (23 men), but with deviations in individual parameters of the neuro-endocrine-immune complex as a manifestation of maladaptation. Upon admission, we determined EKI, as well as BP and neuro-endocrine parameters. After three rehabilitation treatment regimens, all tests were repeated.* ***Results.*** *The EKI initial levels were in the range of 20 ÷ 71.4 %. Their changes in the range of 2.5 % considered as insignificant were reported in 49 cases. However, in 17 patients, EKI levels increased significantly, and in 6 patients decreased. The response of EKI to the application of adaptogenic factors did not depend on its initial levels. Neither the directionality nor the magnitude of EKI responses, nor their absence depended on the nature of treatment regimens. There were both linear (direct and inverse) and nonlinear correlations between changes in EKI and 32 neuro-endocrine variables. Nineteen variables were selected for the regression model: aldosterone; 5 parameters of beta, 4 alpha, 2 delta and 2 theta EEG rhythms, SPD entropy in T3 locus; 3 parameters of HRV, BPS_2/BPS_1 ratio. Changes in this constellation of variables explain 72 % of the variability in EKI changes. The forward stepwise program included in the discriminant model only 24 variables as characteristic. On the other hand, the discriminant analysis method revealed 35 initial variables as predictors of individual EKI responses (classification accuracy 98.6 %). It turned out that using the regression model, it is possible to reliably predict not only the direction/quality of the EKI response, but also its actual value (the standard error for estimation is 2.5 %).* ***Conclusions.*** *The electrokinetic index response to adaptogenic factors are ambiguous and correlate with changes in EEG and HRV variables and aldosterone levels in individuals with maladaptation. Both quality and magnitude of the EKI response are independent of its initial level or the nature of adaptogenic factors, but can be reliably predicted (accuracy 98.6 %) by the constellation of 35 initial neuro-*

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endocrine variables, including 23 EEG and 7 heart rate variables, triiodothyronine, aldosterone and diastolic BP levels, as well as Kerdö vegetative index (KVI) and Popovych adaptation index. These findings suggest that EKI may serve as an integrative biomarker of neuro-endocrine regulation and could be useful for personalized rehabilitation program planning.

Keywords: *electrokinetic index of the buccal epithelium; electroencephalography; heart rate variability; adaptation hormones; multivariate analysis*

Introduction

Previous studies have demonstrated that blood pressure (BP) exhibits distinct qualitative-quantitative clustering patterns, which correlate significantly with age, sex, and a comprehensive constellation of neuro-endocrine, immune, and metabolic variables — a phenomenon was termed the tensioregulome [1–4]. Notably, the electrokinetic index (EKI) of buccal epithelium, which cannot formally be attributed to either neuro-endocrine-immune or metabolic constellations, emerged as a significant component of this regulatory network, showing maximal values in patients with low normal BP and minimal values in those with arterial hypertension stage II, paralleling changes in vagal tone and multiple EEG parameters. Interestingly, patients with low normal BP were the youngest in the sample (43.1 ± 2.1 years old), while patients with AH II were the oldest (61.3 ± 2.5 years old).

This situation is quite natural, because EKI (synonyms: electrokinetic properties of buccal epithelium cell nuclei [5, 6]; percentage of cells with electrophoretically movable nuclei as the value of electronegativity of cell nuclei (ENN) [7]; electrophoretic mobility of cell nuclei (EMN) index [8, 9]) is primarily considered a marker of human biological ages [6, 8, 9] as well as marker of general nonspecific resistance of the human body and changes in energies of an organism provoked by different causes, i.e. tiredness, medical drugs, narcotics consumption, ionizing radiation, etc.; determination of EKI is applied to many areas of medicine, sport and work practice [7, 10, 11]. It has previously been shown that changes in EKI under the influence of even the same factor are ambiguous and have an individual character [12].

Recent advances in understanding cellular electrokinetic properties have revealed their connection to membrane potential and cellular physiology [13]. The ζ-potential, measured a few nanometers from the cell surface, has been shown to play a functional role in various physiological processes, including immune response, cell-cell interactions, and aging [13–15]. However, the relationship between electrokinetic properties of buccal epithelium and systemic neuro-endocrine regulation remains poorly understood. Previous studies have demonstrated sensitivity of EKI to various stress [8] and physical [11] factors, electric field [12, 16], and intensive physical exercise [17, 18], but the underlying mechanisms have not been elucidated.

Research purpose. The purpose of the study is to determine how changes in EKI levels correlate with changes in brain electrical activity and adaptation hormones levels in individuals with maladaptation.

Research problems. What is the relationship between adaptogens caused changes in EKI levels and neuro-endocrine parameters in individuals with maladaptation? Can initial neuro-endocrine parameters serve as predictors of individual reactions on adaptogens?

Research hypotheses. There is a significant correlation between adaptogens caused individual changes in EKI levels and neuro-endocrine parameters in patients with maladaptation. Not only the directionality, but also the magnitude of adaptogens caused changes in EKI are determined by the constellation of parameters of the initial state of the neuro-endocrine status, but not the initial level of EKI and the nature of the adaptogen.

Materials and methods

The study included 72 participants: 42 men (mean age 49 ± 15 years) and 30 women (mean age 51 ± 13 years). The cohort comprised two subgroups: 1) apparently healthy individuals without clinical diagnosis (n = 49), and 2) 23 men with chronic pyelonephritis in stable remission phase (diagnosed according to ICD-10 criteria, with no exacerbations for at least 6 months). Exclusion criteria included: acute inflammatory processes, decompensated chronic diseases, pregnancy, mental disorders, intake of medications affecting autonomic nervous system or hormonal status within 2 weeks prior to examination. The sample size was determined based on power analysis ($\alpha = 0.05$, $\beta = 0.20$, effect size d = 0.6), requiring minimum 64 participants for regression analysis with 20 predictors.

A feature of this study is that it is a kind of meta-analysis of previous studies conducted by us in August 2011, June, September and November 2015, March 2018, and February 2019, using the same equipment. Some fragments were published earlier [19–24].

All participants exhibited subclinical deviations in individual neuro-endocrine-immune parameters (described in detail in previous studies with their participation [1–4, 19–33]), indicative of maladaptation syndrome according to established criteria [34, 35].

At a receipt, we first determined the EKI as rate of electronegative nuclei of buccal epithelium by intracellular microelectrophoresis on the device Biotest (produced by V.N. Karazin Kharkiv National University), according to the method described [5, 7, 10].

Systolic and diastolic BP and HR were measured (by tonometer Omron M4-I, Netherlands) in a sitting position three times in a row followed by calculation the Kerdö vegetative index (KVI) as well as Ps2/Ps1, Ps3/Ps1, Pd2/Pd1, and Pd3/Pd1 ratios [3].

Then we recorded electrocardiogram in II lead to assess the parameters of HRV (by software and hardware complex CardioLab + HRV produced by KhAI-Medica, Kharkiv, Ukraine). For further analysesб the following parameters were selected. Baevsky's parameters [34]: heart rate (HR), mode (Mo), the amplitude of the mode (AMo) and variational scope (MxDMn) as well as Baevsky's stress index (BSI = AMo/2 · Mo · MxDMn) and Baevsky's activity of regulatory systems index (BARSI). Temporal parameters (time domain methods): 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 msec (pNN50); triangular index (TNN). Spectral parameters (frequency domain methods): spectral power density (SPD) 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 and LFnu = 100 % · LF/(LF + HF) [36, 37].

Simultaneously, EEG recorded (by hardware-software complex NeuroCom Standard (KhAI-Medica, Kharkiv, Ukraine)) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10–20 international system, with the reference electrodes A and Ref on the earlobes. Two minutes after the eyes had been closed, 25 sec of artifact free EEG data were collected by computer. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), absolute (μV^2/Hz) and relative (%) SPD of basic rhythms: β (35 ÷ 13 Hz), α (13 ÷ 8 Hz), θ (8 ÷ 4 Hz) and δ (4 ÷ 0.5 Hz) in all loci, according to the instructions of the device. In addition, calculated coefficient of asymmetry (As) and laterality index (LI) for SPD each rhythm using equations [38]:

$$As, \% = 100 \cdot (max - min)/min.$$

$$LI, \% = \Sigma\,[200 \cdot (right - left)/(right + left)]/8.$$

We calculated also for HRV bands and each EEG locus the entropy (h) of normalized SPD using Popovych's [25–27] equations based on classic Shannon's [39] equation:

$$hHRV = -[SPDHF \cdot \log_2 SPDHF + SPDLF \cdot \log_2 SPDLF + SPDVLF \cdot \log_2 SPDVLF + SPDULF \cdot \log_2 SPDULF]/\log_2 4.$$

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

In portion of the capillary blood we counted up leukocytogram and calculated its adaptation index as well as strain index by Popovych [26, 27]:

$$PSI = [(eosinophils/3.5-1)^2 + (band\ neutrophils/3.5-1)^2 + (monocytes/5.5-1)^2 + (leukocytes/6-1)^2]/4.$$

At last, we took venous blood samples for hormonal tests. We determined content of cortisol, aldosterone, testosterone, triiodothyronine and calcitonin (by the ELISA with the use of analyzer RT-2100C and corresponding sets of reagents from Alkor Bio, XEMA Co., Ltd and DRG International Inc.).

Participants were allocated to three rehabilitation regimens based on clinical indications and availability:

— regimen 1 (n = 38, duration 4 days): transcutaneous electrostimulation using VEB device [23, 24, 28, 40];

— regimen 2 (n = 20, duration 7 days): oral intake of Naftussya water (3 mL/kg three times daily, 1 h before meals). Naftussya bioactive water is a main curative factor of the Truskavets Spa, and established adaptogenic properties [27, 40, 41];

— regimen 3 (n = 14, duration 10–11 days): complex balneotherapy including Naftussya bioactive water (as in regimen 2) combined with ozokerite applications (temperature 45 °C, 30 minutes, lumbar area, every other day, 5 procedures) and mineral baths (Cl^-, SO_4^{2-}, Na^+, Mg^{2+} containing salt concentration 25 g/L, temperature 36–37 °C, 10 minutes, every other day, 5 procedures). This comprehensive protocol represents standard spa therapy duration [27, 30, 32, 33]. Naftussya and ozokerite have the same neuro-endocrine-immune effects caused by their aryl hydrocarbons [42].

The different durations reflect established clinical protocols for each modality. All assessments were repeated 24 hours after completion of the respective regimen. Participants maintained their usual diet and physical activity level throughout the study period.

While the non-uniform treatment duration represents a limitation, it allowed us to evaluate EKI responses across different therapeutic modalities and timeframes, more closely reflecting real-world clinical practice. Importantly, our subsequent analysis (Table 1) demonstrated that neither the direction nor magnitude of EKI changes depended on treatment type or duration, suggesting that EKI responses reflect individual adaptive capacity rather than specific therapeutic effects.

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 participants the informed consent is got and used all measures for providing of anonymity of participants.

Statistical processing was performed using a software package Microsoft Excel and Statistica 6.4 StatSoft Inc. (Tulsa, OK, USA). Data were presented as mean ± standard deviation (SD) or mean ± standard error (SE) where indicated. Normality of distribution was assessed using Shapiro-Wilk test. For normally distributed variables, between-group comparisons were performed using independent t-test or one-way ANOVA with post-hoc Tukey HSD test. Non-parametric alternatives (Mann-Whitney U or Kruskal-Wallis test) were applied when normality assumptions were violated.

Definition of EKI response categories: changes in EKI were classified as: 1) significant increase (> +2.5 %), 2) no significant change (± 2.5 %), or 3) significant decrease (< –2.5 %). This threshold was established based on the coefficient of variation for EKI measurements (Cv = 0.25) and corresponds to changes in biological age of approximately one year according to normative data [20–22]. Sensitivity analysis using alternative thresholds (± 5 %, ± 10 %) confirmed the robustness of findings (data not shown).

Correlation and regression analysis: Pearson or Spearman correlation coefficients were calculated depending on data distribution. Discriminant analysis: forward stepwise discriminant function analysis was employed to classify EKI response patterns based on baseline variables. Wilks' lambda, canonical correlations, and classification accuracy were reported. Model performance was assessed using confusion matrix and receiver operating characteristic (ROC) analysis.

Multiple testing correction: given the exploratory nature of correlation screening, we applied a false discovery rate (FDR) correction using the Benjamini-Hochberg procedure for the initial correlation analysis. For subsequent hypothesis-driven analyses (regression and discriminant models), no correction was applied as these represent confirmatory tests of specific hypotheses.

Statistical significance was set at $p < 0.05$ (two-tailed). Effect sizes were reported as R^2 for regression models.

Results

Distribution of EKI baseline values and response patterns

Baseline EKI values ranged from 20 to 71.4 % (mean 43.8 ± 12.1 %, median 44.5 %), showing normal distribution (Shapiro-Wilk test, $p = 0.18$).

Following rehabilitation interventions, EKI responses were heterogeneous (Fig. 1):

— no significant change (± 2.5 %): n = 49 (68.1 %), mean change +0.3 ± 1.4 %;

— significant increase (> +2.5 %): n = 17 (23.6 %), mean change +4.8 ± 1.6 %, range +2.6 to +8.5 %;

— significant decrease (< –2.5 %): n = 6 (8.3 %), mean change –4.1 ± 1.2 %, range –2.8 to –6.2 %.

In the next stage of the analysis, the actual (V) values of EKI were normalized by formula [43]: $Z = (V/N - 1)/Cv$, where N is normal level for each age, Cv is coefficient of its variation (0.25). Age norms were calculated using the formula: NEKI = (82.656 – age)/0.80476, which we derived based on the graph in the instructions for the Biotest device.

Importantly, the magnitude and direction of EKI response were independent of baseline EKI values (Fig. 1, bottom panel: $r = 0.08$, $p = 0.51$ for absolute values; $r = 0.11$, $p = 0.36$ for normalized values), suggesting that individual response patterns reflect intrinsic adaptive capacity rather than regression to the mean. One-way ANOVA confirmed significant differences in EKI changes between the three response groups ($F_{(2.69)} = 156.3$, $p < 0.001$, $\eta^2 = 0.82$), validating our classification approach.

Moreover, EKI responses to electrical stimulation were found to be almost identical in studies conducted in 2015, 2018, and 2019 (Table 1).

Neuro-endocrine determinants of EKI changes: multiple regression analysis

At the next stage, a screening of correlations between changes in EKI and the registered parameters was carried out. Screening identified 32 variables showing significant bivariate correlations with EKI changes. These variables were entered into stepwise multiple regression analysis. The final model retained 19 predictors (Table 2, Fig. 2), explaining 72 % of variance in EKI changes ($R = 0.848$, $R^2 = 0.720$, adjusted $R^2 = 0.610$, $F_{(19,5)} = 7.0$, $p < 10^{-6}$, SE = 1.5 %).

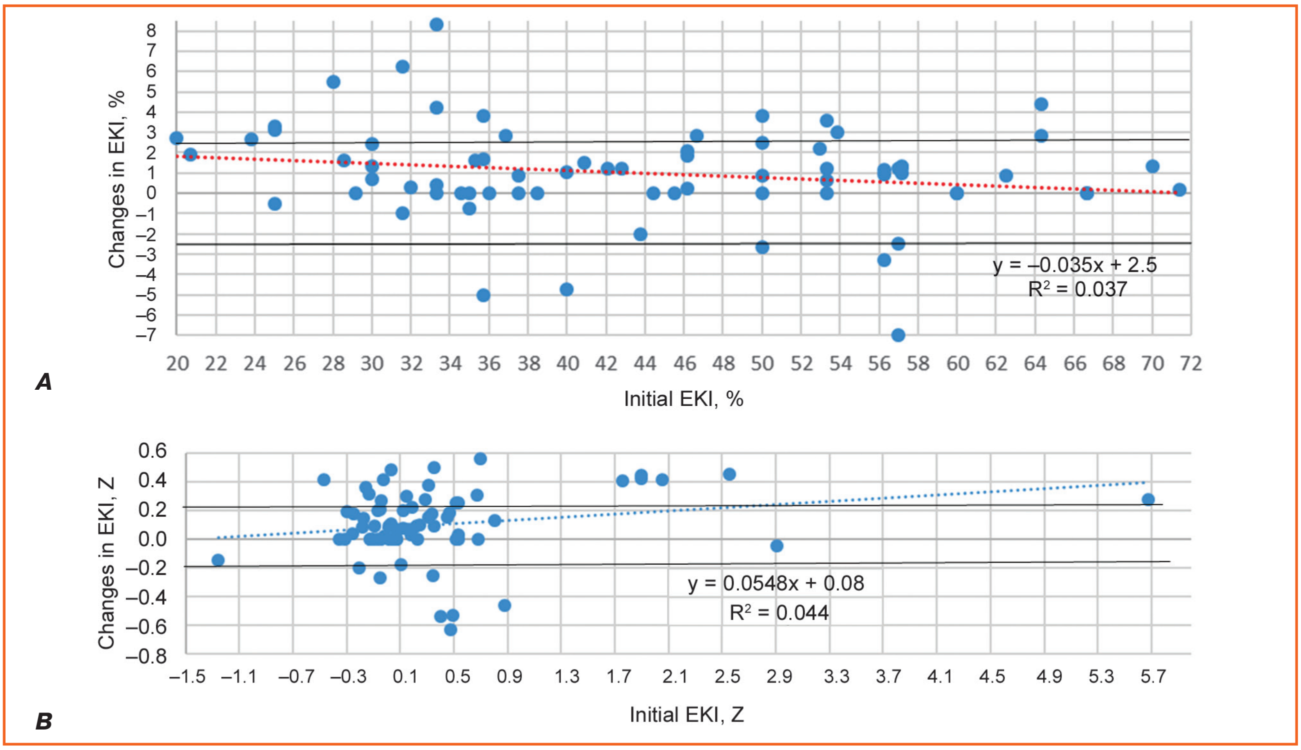

Figure 1. Relationship between initial EKI and its changes following rehabilitation treatment: A — actual EKI values; B — age-normalized Z-scores. Each point represents one patient (n = 72). Dashed horizontal lines indicate the threshold for significant changes (± 2.5 %). The absence of correlation (r = 0.08, p = 0.51 for actual values; r = 0.11, p = 0.36 for normalized values) demonstrates that EKI responses are independent of initial levels

Cross-validation using leave-one-out procedure yielded similar predictive accuracy ($R^2cv = 0.68$), confirming model stability. Variance inflation factors (VIF) ranged from 1.3 to 2.8, indicating acceptable multicollinearity levels. Residual analysis showed normal distribution (Shapiro-Wilk $p = 0.24$) and homoscedasticity (Breusch-Pagan $p = 0.31$), confirming model assumptions were met.

The model revealed several key findings:

1. Theta rhythm in T3 locus emerged as the strongest predictor (beta = –0.609), with higher theta SPD associated with decreased EKI. This temporal lobe region is involved in memory and emotional processing, suggesting a link between cognitive-emotional state and cellular electrokinetic properties.

2. Aldosterone showed negative association (beta = = –0.219), indicating that higher mineralocorticoid activity corresponds to decreased EKI responses. This may reflect the role of aldosterone in cellular ion homeostasis and membrane potential regulation.

3. HRV parameters (VLF SPD, LF/HF ratio) contributed significantly, confirming the involvement of autonomic regulation in EKI modulation.

4. Multiple EEG parameters from beta, alpha, delta, and theta bands across different cortical regions were included, suggesting that EKI reflects integrated brain electrical activity rather than localized processes

5. The BPS_2/BPS_1 ratio, reflecting blood pressure reactivity, was included in the model, suggesting a link between EKI and cardiovascular regulation.

Another approach to elucidating the neuro-endocrine accompaniment of EKI responses to adaptogenic factors

Table 1. Variants of influence (mean ± SE) of adaptogenic factors on EKI

Factor	n	dEKI ± 2.5 %	n	dEKI > +2.5 %	n	dEKI < –2.5 %
Electrostimulation by VEB	24	0.65 ± 0.12	9	4.3 ± 0.6	5	–4.5 ± 0.9
In June and September 2015	11	0.4 ± 0.3	6	3.7 ± 0.4	4	–4.8 ± 0.9
In March 2018	7	0.8 ± 0.3	0	–	0	–
In February 2019	6	0.9 ± 0.3	3	5.5 ± 1.4	1	–2.6
Naftussya in November 2015	14	0.9 ± 0.2	5	3.6 ± 0.7	1	–3.3
Balneocomplex in August 2011	11	0.35 ± 0.25	3	3.0 ± 0.4	0	–

Table 2. Regression summary for change in EKI

N = 72		Beta	St. err. of beta	B	St. err. of B	$t_{(51)}$	p-level
Variables	r		Intercept	0.810	0.212	3.82	10^{-3}
Deviation-θ, Hz	**0.31**	0.512	0.095	1.551	0.288	5.39	10^{-5}
SPD VLF, %	**0.27**	0.117	0.102	0.016	0.014	1.15	0.254
P4-δ SPD, μV²/Hz	**0.24**	0.247	0.105	0.002	0.001	2.35	0.023
O1-β SPD, μV²/Hz	**0.24**	0.416	0.139	0.015	0.005	2.99	0.004
Asymmetry-δ, %	**0.21**	0.344	0.087	0.023	0.006	3.94	10^{-4}
Fp1-β SPD, μV²/Hz	**0.20**	–0.392	0.124	–0.020	0.006	–3.16	0.003
T4-β SPD, μV²/Hz	**0.20**	–0.220	0.103	–0.005	0.002	–2.12	0.039
P4-β SPD, μV²/Hz	**0.20**	0.264	0.158	0.012	0.007	1.67	0.100
F7-β SPD, %	**0.18**	0.206	0.093	0.026	0.012	2.22	0.031
BPS_2/BPS_1 ratio	**0.18**	0.111	0.085	2.146	1.644	1.30	0.198
Frequency-α, Hz	**0.17**	0.222	0.088	0.563	0.224	2.51	0.015
SPD VLF, msec²	**0.16**	–0.128	0.098	–0.000	0.000	–1.30	0.198
T3-θ SPD, %	**–0.25**	–0.609	0.122	–0.277	0.056	–4.98	10^{-5}
LF/HF ratio	**–0.22**	–0.376	0.098	–0.129	0.034	–3.85	10^{-4}
Laterality-α, %	**–0.20**	–0.261	0.101	–0.014	0.005	–2.59	0.013
P4-α SPD, %	**–0.20**	–0.075	0.104	–0.014	0.019	–0.72	0.474
T3 SPD entropy	**–0.19**	0.513	0.129	6.262	1.572	3.98	10^{-4}
Aldosterone, pM/L	**–0.19**	–0.219	0.094	–0.015	0.007	–2.34	0.023
P4-α SPD, μV²/Hz	**–0.17**	–0.495	0.155	–0.005	0.001	–3.19	0.002

***Notes:** $R = 0.848$; $R^2 = 0.720$; adjusted $R^2 = 0.610$; $F_{(20.5)} = 6.6$; $p < 10^{-6}$; SE = 1.5 %.*

was to construct profiles of those variables that changed significantly under at least one variant of EKI changes (Fig. 3).

Therefore, there were both linear (direct and inverse) and nonlinear correlations between changes in EKI and the registered neuro-endocrine variables.

Patterns of concomitant neuro-endocrine changes: cluster analysis

To better understand the coordinated changes in neuro-endocrine parameters accompanying different EKI responses, we performed hierarchical cluster analysis on Z-transformed variables that showed significant changes in at least one EKI response group (Fig. 4). Seven distinct clusters emerged, each representing a specific pattern of coordinated regulation.

Cluster 1 (beta rhythm amplitude — F4, T4 loci): these parameters showed the most congruent changes with EKI across all response categories (correlation with EKI change: $r = 0.68$, $p < 0.001$). This may reflect the influence of autonomic nervous system, as these cortical areas are involved in autonomic regulation [44, 45]. This suggests that right-hemisphere beta activity, associated with cognitive control and attention, is tightly coupled with cellular electrokinetic properties.

Cluster 2 (VLF HRV and theta deviation): variables in this cluster increased proportionally with EKI increases but showed disproportionately large decreases when EKI decreased (asymmetry index = 2.3). This pattern suggests a threshold effect, where downward EKI shifts may trigger more pronounced autonomic and cortical changes.

Cluster 3 (alpha frequency and frontal-central beta SPD): these parameters decreased with EKI decreases but remained unchanged with EKI increases or stability, suggesting they may represent protective mechanisms that are compromised only under maladaptive conditions.

Cluster 4 (LF HRV and multiple EEG parameters): showing inverse relationship with cluster 2, these variables increased with EKI decreases, possibly representing compensatory activation of sympathetic tone and cortical arousal.

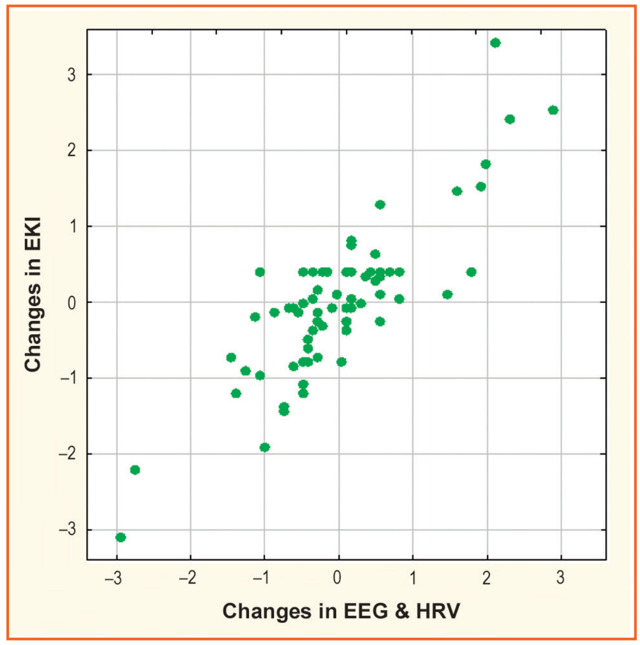

Figure 2. Scatterplot of canonical correlation between changes in neuro-endocrine variables (X-line) and electrokinetic index (Y-line)

Notes: $R = 0.848$; $R^2 = 0.720$; $\chi^2_{(22)} = 73$; $p < 10^{-6}$; Λ prime = 0.289.

Cluster 5 (aldosterone and sympathetic markers): the coordinated increase of aldosterone with sympathetic HRV markers and specific EEG parameters only during EKI increases suggests activation of stress-responsive neuro-endocrine axes during adaptive cellular responses.

Cluster 6 (laterality indices of theta and delta): these parameters increased both with EKI increases and decreases, but decreased when EKI remained stable.

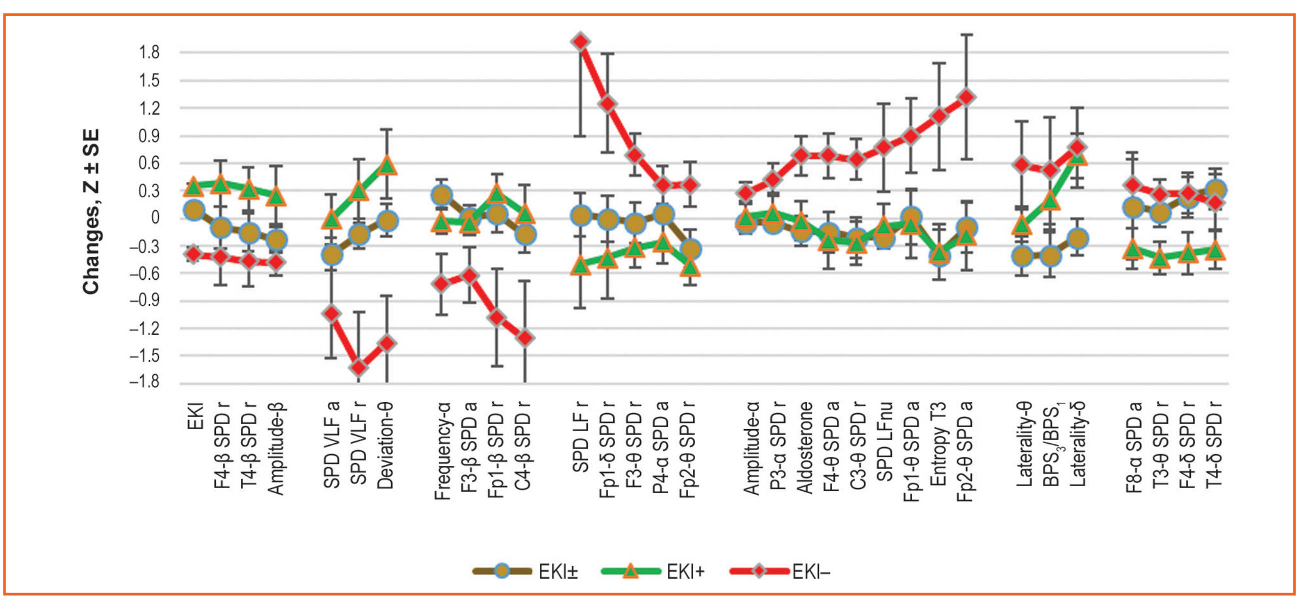

Figure 3. Profiles of concomitant changes in registered variables in individuals with different EKI responses to adaptogenic factors

Table 3. Discriminant function analysis summary for changes in neuro-endocrine variables

Variables currently in the model	Changes in EKI (n)			Parameters of Wilks' statistics				
	± 2.5 % (49)	> +2.5 % (17)	< −2.5 % (6)	Wilks' Λ	Partial Λ	F-remove (2,46)	p-level	Tolerance
SPD VLF, %	−2.5 2.1	4.3 4.5	−23.0 8.8	0.156	0.941	1.45	0.245	0.206
SPD LF, %	1.2 2.1	−4.3 3.8	18.3 9.5	0.162	0.908	2.34	0.108	0.152
SPD LFnu, %	−3.0 1.6	−1.2 3.5	11.5 7.4	0.176	0.833	4.61	0.015	0.319
Laterality-δ, %	8 8	27 10	31 17	0.196	0.747	7.79	0.001	0.221
Fp1-δ SPD, %	−0.1 4.0	−6.9 7.2	20.2 8.8	0.185	0.792	6.02	0.005	0.225
F4-δ SPD, %	4.5 4.3	−7.4 4.4	5.2 4.2	0.155	0.949	1.24	0.298	0.133
T4-δ SPD, %	6.1 4.2	−6.6 3.9	3.3 2.5	0.165	0.890	2.84	0.068	0.436
Deviation-θ, Hz	−0.01 0.10	0.32 0.21	−0.75 0.28	0.196	0.747	7.78	0.001	0.428
Laterality-θ, %	−16 8	−3 7	23 17	0.172	0.851	4.04	0.024	0.199
Fp1-θ SPD, μV²/Hz	0 7	−1 9	21 9	0.167	0.879	3.16	0.052	0.156
Fp2-θ SPD, μV²/Hz	−3 7	−5 10	36 18	0.161	0.913	2.18	0.125	0.161
Fp2-θ SPD, %	−2.0 1.2	−3.2 1.3	2.3 1.5	0.169	0.868	3.50	0.038	0.135
F3-θ SPD, %	−0.3 1.3	−1.9 1.3	4.0 1.6	0.174	0.843	4.27	0.020	0.182
T3-θ SPD, %	0.3 0.8	−2.1 0.9	1.3 0.7	0.178	0.824	4.90	0.012	0.261
Frequency-α, Hz	0.24 0.14	−0.03 0.13	−0.67 0.31	0.171	0.857	3.83	0.029	0.666
Amplitude-α, μV	−0.6 0.7	0.1 1.9	2.9 1.3	0.177	0.830	4.72	0.014	0.158
P3-α SPD, %	−1.1 2.1	1.2 4.3	8.8 3.8	0.162	0.904	2.44	0.098	0.539
P4-α SPD, μV²/Hz	20 29	−97 89	139 81	0.196	0.748	7.74	0.001	0.192
Amplitude-β, μV	−0.8 0.5	0.9 1.1	−1.7 0.5	0.154	0.951	1.18	0.317	0.295
F3-β SPD, μV²/Hz	0 7	−3 7	−33 16	0.161	0.914	2.17	0.126	0.279
F4-β SPD, %	−1.2 2.8	4.6 3.0	−5.1 3.7	0.168	0.871	3.40	0.042	0.076
C4-β SPD, %	−1.8 2.1	0.6 3.2	−13.7 6.5	0.154	0.954	1.12	0.336	0.234
Entropy SPD T3	−0.04 0.03	−0.04 0.03	0.12 0.06	0.179	0.821	5.01	0.011	0.242
BPS_3/BPS_1 ratio · 10^3	−30 18	15 25	39 43	0.155	0.948	1.27	0.291	0.518
SPD VLF, $msec^2$	−248 127	2 184	−705 332	0.143	0.977	0.54	0.588	0.536
F4-θ SPD, μV²/Hz	−7 10	−11 14	31 11	0.145	0.987	0.31	0.738	0.144
C3-θ SPD, %	−1.0 1.0	−1.3 1.1	3.0 1.0	0.146	0.994	0.14	0.869	0.219
F8-α SPD, μV²/Hz	7 29	−17 11	18 14	0.145	0.991	0.20	0.820	0.458
Fp1-β SPD, %	0.7 2.8	3.7 2.9	−14.8 7.3	0.142	0.966	0.80	0.458	0.107
T4-β SPD, %	−2.3 3.1	4.7 3.5	−7.0 4.2	0.143	0.975	0.57	0.572	0.115
Aldosterone, pM/L	−6.3 6.8	−1.3 4.6	30.2 9.5	0.145	0.966	0.50	0.570	0.450

Notes: step 24, N of vars in model: 24; grouping: 3 groups. Wilks' Λ: 0.1467; approx. $F_{(49)} = 3.1$; $p = 10^{-6}$.

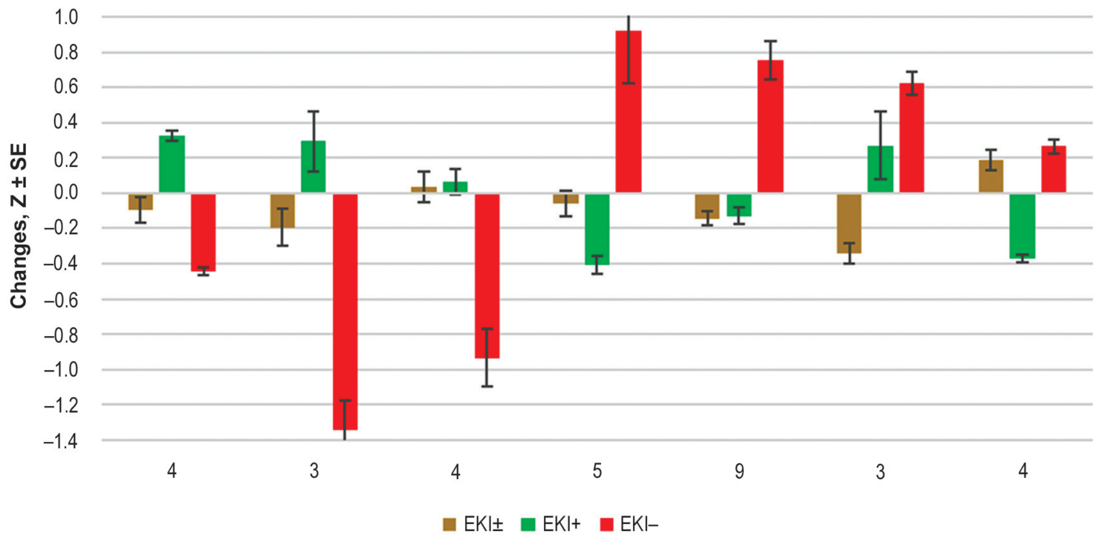

Figure 4. Clusters of concomitant changes in registered variables in individuals with different EKI responses to adaptogenic factors

Table 4. Summary of stepwise analysis for changes in variables, ranked by criterion Λ

Variables currently in the model	F to enter	p-level	Λ	F-value	p-level
SPD VLF, %	5.99	0.004	0.852	5.99	0.004
Laterality-δ, %	3.89	0.025	0.765	4.89	0.001
T4-δ SPD, %	3.19	0.047	0.698	4.40	0.0004
Deviation-θ, Hz	3.28	0.044	0.635	4.21	0.0002
Frequency-α, Hz	4.02	0.023	0.565	4.30	10^{-4}
Fp1-δ SPD, %	4.09	0.021	0.501	4.40	10^{-5}
T3-θ SPD, %	2.34	0.105	0.466	4.18	10^{-5}
Entropy SPD T3	2.99	0.057	0.425	4.14	10^{-5}
Laterality-θ, %	2.47	0.093	0.393	4.03	10^{-5}
F4-δ SPD, %	1.48	0.235	0.375	3.80	10^{-5}
P3-α SPD, %	1.45	0.243	0.357	3.61	10^{-5}
SPD LFnu, %	1.30	0.281	0.342	3.43	10^{-5}
Fp1-θ SPD, μV²/Hz	1.74	0.184	0.322	3.34	10^{-5}
BPS_3/BPS_1 ratio	1.08	0.348	0.310	3.18	10^{-5}
F3-θ SPD, %	1.05	0.357	0.299	3.04	10^{-5}
Fp2-θ SPD, %	1.60	0.211	0.282	2.98	10^{-5}
F4-β SPD, %	1.59	0.213	0.266	2.93	10^{-5}
Fp2-θ SPD, μV²/Hz	1.60	0.211	0.251	2.88	10^{-5}
F3-β SPD, μV²/Hz	1.81	0.174	0.234	2.86	10^{-5}
Amplitude-β, μV	2.55	0.088	0.212	2.92	10^{-5}
P4-α SPD, μV²/Hz	2.36	0.105	0.194	2.97	10^{-5}
Amplitude-α, μV	3.43	0.041	0.170	3.12	10^{-5}
SPD LF, %	2.39	0.102	0.154	3.17	10^{-6}
C4-β SPD, %	1.12	0.336	0.147	3.09	10^{-6}

The leftward shift in theta-delta symmetry may reflect hemispheric reorganization during adaptive processes, regardless of direction.

Cluster 7 (mixed parameters): variables showing complex non-linear relationships with EKI changes, requiring further investigation.

This clustering reveals that EKI changes are embedded within coordinated neuro-endocrine response patterns, rather than being isolated cellular phenomena.

In order to identify variables, the changes of which characteristic for different variants of changes in the electrokinetic index, discriminant analysis was conducted [46]. The forward stepwise program included only 24 variables in the discriminant model (Tables 3, 4). Another 8 variables were found to be out of the model, despite the clear recognition ability probably, due to duplication or redundancy of information.

However, the main goal of discriminant analysis was to visualize the individual responses of the registered variables to adaptogenic factors. This goal was achieved by calculating individual values of discriminant roots based on raw coefficients and constants (Table 5).

Table 6 presents the full structural coefficients and average values (centroids) of roots as well as changes in variables, both included and not included in the model.

Table 5. Parameters of Wilks' statistics for discriminant variables

Coefficients	Standardized		Raw	
Variables currently in the model	Root 1	Root 2	Root 1	Root 2
SPD VLF, %	–0.656	–0.033	–0.039	–0.002
Laterality-δ, %	0.955	–0.981	0.018	–0.019
T4-δ SPD, %	–0.609	0.089	–0.024	0.003
Deviation-θ, Hz	–0.233	–0.996	–0.313	–1.340
Frequency-α, Hz	–0.422	–0.413	–0.466	–0.456
Fp1-δ SPD, %	1.045	0.586	0.037	0.021
T3-θ SPD, %	–0.793	0.675	–0.154	0.131
Entropy SPD T3	0.986	–0.405	5.166	–2.124
Laterality-θ, %	–0.641	0.924	–0.013	0.018
F4-δ SPD, %	0.100	0.824	0.004	0.031
P3-α SPD, %	0.212	0.515	0.014	0.034
SPD LFnu, %	0.880	0.108	0.069	0.008
Fp1-θ SPD, μV²/Hz	0.756	0.839	0.017	0.019
BPS_3/BPS_1 ratio	0.230	–0.342	1.917	–2.844
F3-θ SPD, %	–1.114	0.244	–0.137	0.030
Fp2-θ SPD, %	1.085	0.584	0.143	0.077
F4-β SPD, %	0.532	1.644	0.030	0.094
Fp2-θ SPD, μV²/Hz	–0.211	–0.953	–0.004	–0.019
F3-β SPD, μV²/Hz	–0.640	–0.250	–0.014	–0.005
Amplitude-β, μV	0.494	–0.064	0.132	–0.017
P4-α SPD, μV²/Hz	–1.241	0.717	–0.005	0.003
Amplitude-α, μV	1.094	–0.706	0.195	–0.126
SPD LF, %	–0.943	0.171	–0.061	0.011
C4-β SPD, %	–0.129	–0.577	–0.009	–0.040
	Constants		0.392	0.142
	Eigenvalues		2.004	1.269
	Canonical R		0.817	0.748
	Wilks' Λ		0.147	0.441
	χ^2		110	47
	Degree freedom		48	23
	p		10^{-6}	0.002
Cumulative proportions			0.612	1

As we can see (Fig. 5), along the major root axis, which contains 61 % of discriminative information, the far right zone is occupied by patients whose EKI significantly decreased. Such localization reflects, on the one hand, a concomitant increase in sympathetic tone, post-occlusive reactivity of systolic BP, entropy of SPD in T3 locus, amplitude of alpha rhythm and its SPD in P3 locus as well as a rightward shift of symmetry of SPD of delta and theta rhythms, while on the other hand, a decrease in the frequency of alpha rhythm and SPD of beta rhythm in F3 locus (Table 6). The polar position is occupied by individuals whose EKI did not change significantly. This reflects minimal, but opposite in sign, changes in the listed parameters. The intermediate position of individuals whose EKI increased significantly reflects, as a rule, intermediate changes in these parameters.

Additional delineation of patients with opposite EKI responses to adaptogenic factors occurs along the minor root axis. The lowest position of patients in whom EKI increased reflects a slight, but maximum for the sample, decrease in variables related to the root positively, and a slight, but maximum for the sample, increase in variables related to the root negatively. On the other hand, the top position of patients in whom EKI decreased reflects the maximum for the sample increase/decrease in these parameters.

Table 6. Correlations variables-canonical roots, means of roots and changes in variables Z-score

Change in variables	Correlations Variables-roots		EKI ± 2.5 %	EKI > +2.5 %	EKI < –2.5 %
Root 1 (61.2 %)	**Root 1**	**Root 2**	**–0.90**	1.47	**3.21**
Laterality-δ	**0.229**	–0.078	**–0.21 ± 0.20**	0.68 ± 0.24	**0.77 ± 0.43**
SPD LFnu	**0.183**	0.161	**–0.21 ± 0.12**	–0.08 ± 0.24	**0.77 ± 0.48**
Laterality-θ	**0.153**	0.056	**–0.41 ± 0.21**	–0.07 ± 0.19	**0.58 ± 0.48**
BPS_3/BPS_1 ratio	**0.149**	–0.014	**–0.40 ± 0.24**	0.20 ± 0.33	**0.52 ± 0.58**
Entropy SPD T3	**0.125**	0.150	**–0.40 ± 0.27**	–0.37 ± 0.30	**1.11 ± 0.58**
P3-α SPD relative	**0.119**	0.070	**–0.05 ± 0.10**	0.06 ± 0.21	**0.42 ± 0.18**
Amplitude-α	**0.108**	0.074	**–0.05 ± 0.06**	0.01 ± 0.18	**0.27 ± 0.12**
Frequency-α, Hz	**–0.195**	–0.087	**0.26 ± 0.13**	–0.03 ± 0.14	**–0.72 ± 0.33**
F3-β SPD a	**–0.114**	–0.110	**0.01 ± 0.13**	–0.05 ± 0.13	**–0.62 ± 0.30**
Root 2 (38.8 %)	**Root 1**	**Root 2**	0.23	**–1.60**	**2.62**
SPD LF r	0.089	**0.309**	0.04 ± 0.24	**–0.50 ± 0.48**	**1.92 ± 1.03**
P4-α SPD a	–0.018	**0.229**	0.05 ± 0.08	**–0.26 ± 0.23**	**0.36 ± 0.21**
F8-α SPD a			0.13 ± 0.58	**–0.33 ± 0.22**	**0.36 ± 0.29**
Fp1-δ SPD r	0.057	**0.206**	0.00 ± 0.25	**–0.43 ± 0.44**	**1.25 ± 0.54**
T3-θ SPD r	–0.059	**0.176**	0.07 ± 0.17	**–0.43 ± 0.18**	**0.26 ± 0.16**
F3-θ SPD r	0.039	**0.156**	–0.05 ± 0.22	**–0.32 ± 0.22**	**0.69 ± 0.23**
F4-θ SPD a			–0.15 ± 0.22	**–0.24 ± 0.31**	**0.68 ± 0.24**
C3-θ SPD r			–0.21 ± 0.22	**–0.27 ± 0.24**	**0.64 ± 0.22**
Fp2-θ SPD a	0.099	**0.155**	–0.10 ± 0.27	**–0.19 ± 0.38**	**1.32 ± 0.68**
Fp2-θ SPD r	0.052	**0.150**	–0.33 ± 0.20	**–0.52 ± 0.21**	**0.37 ± 0.24**
F4-δ SPD r	–0.077	**0.144**	0.23 ± 0.22	**–0.38 ± 0.23**	**0.27 ± 0.22**
T4-δ SPD r	–0.105	**0.135**	0.32 ± 0.22	**–0.34 ± 0.21**	**0.17 ± 0.31**
Fp1-θ SPD a	0.056	**0.094**	0.02 ± 0.30	**–0.06 ± 0.37**	**0.90 ± 0.40**
Aldosterone			–0.14 ± 0.16	**–0.03 ± 0.10**	**0.68 ± 0.21**
SPD VLF r	–0.096	**–0.349**	–0.17 ± 0.16	**0.30 ± 0.35**	**–1.63 ± 0.60**
SPD VLF a			–0.39 ± 0.18	**–0.01 ± 0.27**	**–1.04 ± 0.48**
Deviation-θ	–0.057	**–0.319**	–0.02 ± 0.18	**0.59 ± 0.37**	**–1.36 ± 0.51**
C4-β SPD r	–0.086	**–0.200**	–0.17 ± 0.20	**0.06 ± 0.30**	**–1.31 ± 0.62**
Amplitude-β	0.049	**–0.185**	–0.23 ± 0.14	**0.25 ± 0.32**	**–0.48 ± 0.14**
F4-β SPD r	0.030	**–0.144**	–0.10 ± 0.23	**0.38 ± 0.25**	**–0.42 ± 0.31**
T4-β SPD r			–0.15 ± 0.21	**0.32 ± 0.24**	**–0.47 ± 0.28**
Fp1-β SPD r			0.05 ± 0.20	**0.27 ± 0.21**	**–1.08 ± 0.53**

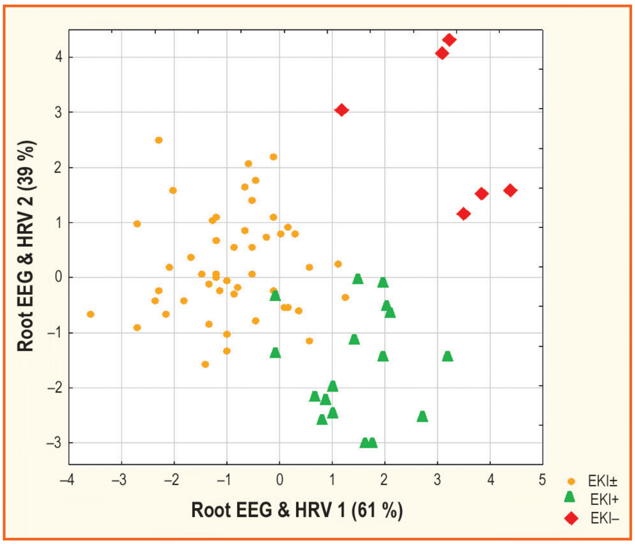

Figure 5. Individual values of discriminant roots of changes in parameters characteristic of different variants of changes in the electrokinetic index

Overall, in the information space of the two discriminant roots, the demarcation of the three clusters of reactions to adaptogenic factors, despite some mixing, is quite clear. The visual impression is documented by both the calculation of Mahalanobis distances (Table 7) and classification functions (Table 8), which revealed only 4 errors in classification (Table 9).

Thus, the three identified variants of EKI responses to adaptogenic factors were accompanied by characteristic changes in the constellation of neuro-endocrine variables.

It is time to move on to the analysis of the possibility of predicting this or that reaction.

Prediction of individual EKI responses: discriminant function analysis

Model development. Following the adopted algorithm, a constellation of initial variables was first selected, which were significantly different at least between the two groups (Fig. 6).

Next, the selected predictors were grouped into 10 clusters containing from 1 to 11 variables (Fig. 7).

The following discriminant analysis formally demonstrated that almost all selected predictors are characteristic (Tables 10, 11). The final model included 35 predictors and generated two discriminant functions (Table 12):

— root 1 (77.4 % of discriminative variance): eigenvalue = 4.615, canonical R = 0.907, primarily distinguished patients with EKI decreases from others;

— root 2 (22.6 % of discriminative variance): eigenvalue = 1.345, canonical R = 0.757, further separated patients with EKI increases from those with stable EKI.

The model achieved excellent discrimination (Wilks' $\Lambda = 0.076$, $\chi^2_{(70)} = 134$, $p < 10^{-5}$) and classification accuracy of 98.6 %, with only one misclassification (one patient with stable EKI predicted to have increase).

Key predictors. Analysis of structure coefficients (Table 13) revealed the most important baseline predictors.

For root 1 (predicting EKI decrease/increase vs. stability):

— Kerdö vegetative index: higher sympathetic dominance predicted EKI decreases;

Table 7. Squared Mahalanobis distances between clusters of change (above the diagonal) and F-values (df = 24.5) and p-levels (under the diagonal)

Clusters of change	EKI ± 2.5 %	EKI > +2.5 %	EKI < –2.5 %
EKI ± 2.5 %	0	9.0	22.6
EKI > +2.5 %	3.2 **0.0004**	0	20.8
EKI < –2.5 %	3.4 **0.0002**	2.6 **0.003**	0

Table 8. Coefficients and constants for classification functions for clusters of change in EKI

Clusters	EKI ± 2.5 %	EKI > 2.5 %	EKI < –2.5 %
Variables currently in the model	p = 0.681	p = 0.236	p = 0.083
SPD VLF, %	0.021	–0.069	–0.145
Laterality-δ, %	–0.017	0.062	0.014
T4-δ SPD, %	0.026	–0.037	–0.064
Deviation-θ, Hz	0.410	2.129	–4.073
Frequency-α, Hz	0.745	0.479	–2.256
Fp1-δ SPD, %	–0.062	–0.012	0.142
T3-θ SPD, %	0.215	–0.391	–0.105
Entropy SPD T3	–7.844	8.310	8.311
Laterality-θ, %	0.009	–0.054	0.001
F4-δ SPD, %	–0.009	–0.057	0.080
P3-α SPD, %	–0.030	–0.059	0.108
SPD LFnu, %	–0.116	0.032	0.187
Fp1-θ SPD, μV²/Hz	–0.010	–0.005	0.102
BPS_3/BPS_1 ratio	–2.472	7.298	–1.382
F3-θ SPD, %	0.256	–0.126	–0.237
Fp2-θ SPD, %	–0.328	–0.129	0.446
F4-β SPD, %	–0.019	–0.119	0.329
Fp2-θ SPD, μV²/Hz	0.002	0.027	–0.061
F3-β SPD, μV²/Hz	0.009	–0.014	–0.061
Amplitude-β, μV	–0.211	0.135	0.293
P4-α SPD, μV²/Hz	0.008	–0.009	–0.006
Amplitude-α, μV	–0.277	0.416	0.223
SPD LF, %	0.077	–0.087	–0.146
C4-β SPD, %	–0.033	0.019	–0.165
Constants	–1.557	–3.874	–9.844

Table 9. Classification matrix. Rows: observed classifications; columns: predicted classifications

Cluster	Percent correct	EKI ± 2.5 %	EKI > 2.5 %	EKI < –2.5 %
EKI ± 2.5 %	95.9	**47**	2	0
EKI > 2.5 %	88.2	2	**15**	0
EKI < –2.5 %	100	0	0	6
Total	94.4	49	17	**6**

— 1/mode HRV ratio: higher circulating catecholamines predicted EKI decreases;

— BARSI: higher regulatory stress predicted EKI decreases;

— F3 & C3-β SPD: lower activity predicted EKI increases;

— HF band SPD: lower vagal tone predicted EKI decreases;

— HF/LF ratio: lower parasympathetic dominance predicted EKI decreases.

For root 2 (distinguishing EKI decrease vs. stability):

— aldosterone: lower level predicted EKI decreases;

— Popovych adaptation index (PAI): lower level predicted EKI decreases;

— T3 & T4-θ SPD: lower activity predicted EKI decreases;

— BSI: higher level predicted EKI stability;

— amplitude mode: higher sympathetic tone predicted EKI stability;

— BP diastolic: higher level predicted EKI stability;

— amplitude-θ and O2-θ SPD: higher level predicted EKI stability;

— triiodothyronine: normal but maximal for sample level predicted EKI stability.

Fig. 8 visualizes, and Tables 13, 14 document, a clear demarcation of the initial states of the neuro-endocrine constellation of patients whose EKI responded differently to adaptogenic factors.

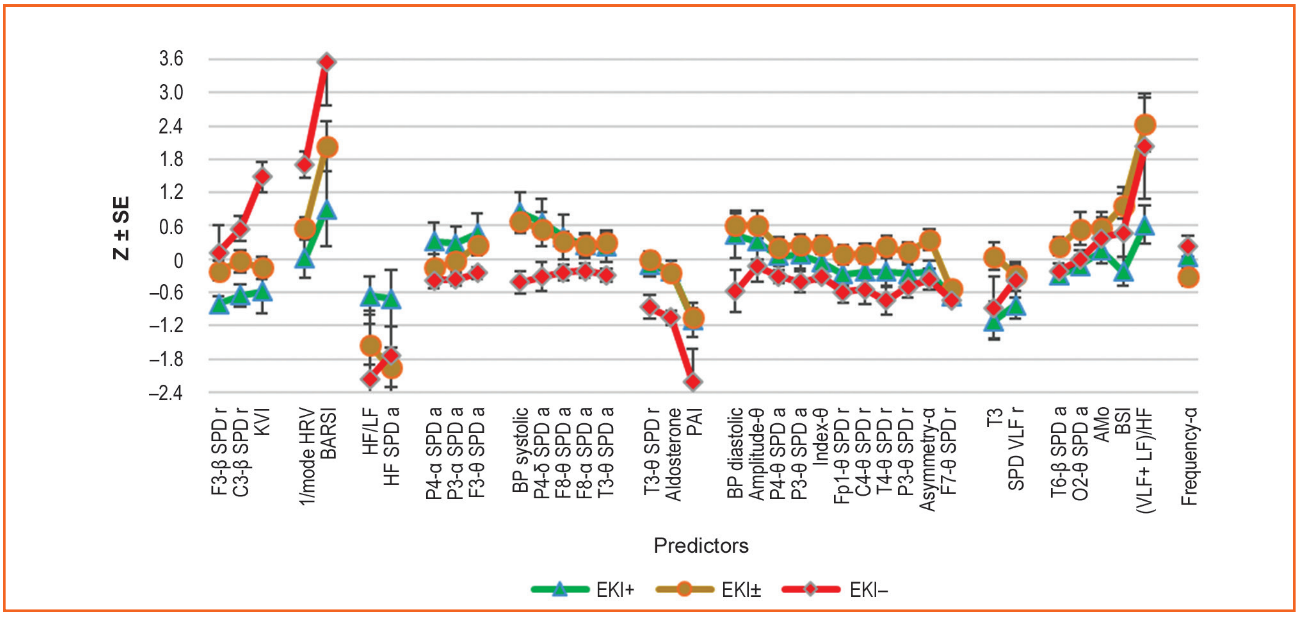

Figure 6. Profiles of registered variables as predictors of different EKI responses to adaptogenic factors

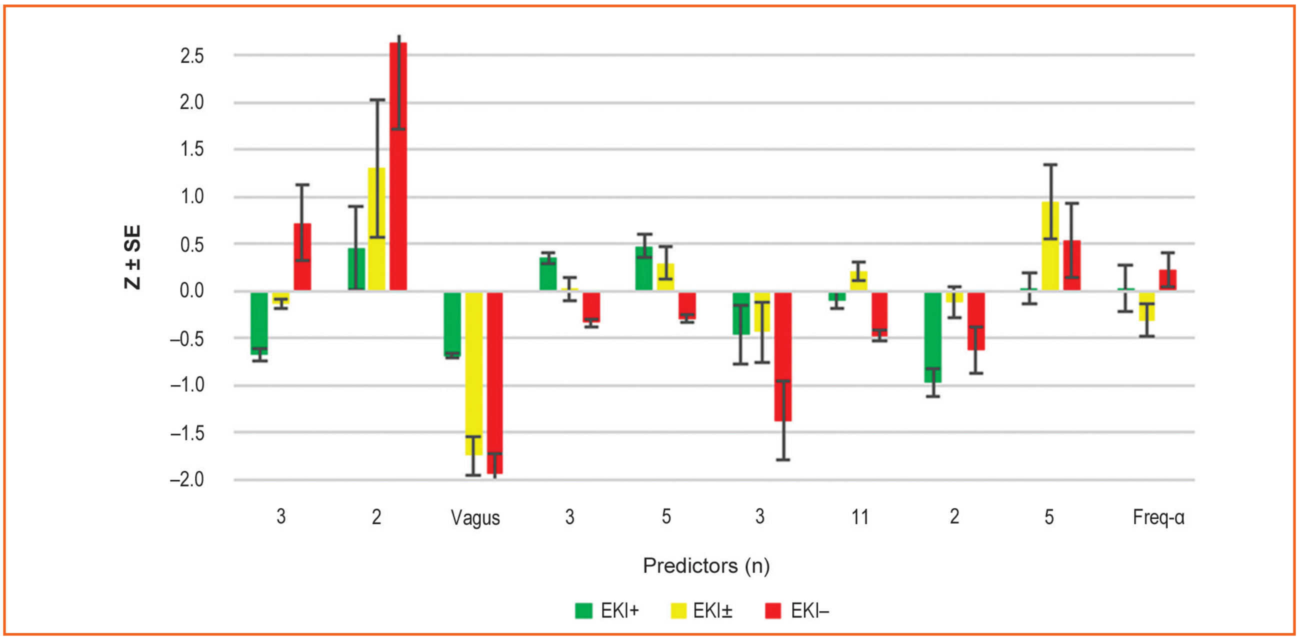

Figure 7. Clusters of registered variables as predictors of different EKI responses to adaptogenic factors

Table 10. Discriminant function analysis summary for predicting variables

Variables as predictors of change in EKI currently in the model	Changes in EKI (n)			Wilks' Λ	Partial Λ	F-remove (2,35)	p-level	Tolerance	Reference (112)	Cv SD
	> +2.5 % (17)	± 2.5 % (49)	< –2.5 % (6)							
F3-β SPD, %	16.8	24.1	28.2	0.082	0.925	1.42	0.256	0.223	26.7	0.463
C3-β SPD, %	18.5	25.1	31.3	0.079	0.956	0.81	0.453	0.282	25.4	0.420
T6-β SPD, μV²/Hz	52	91	59	0.101	0.751	5.79	0.007	0.425	74	0.980
Frequency-α, Hz	10.65	10.33	10.83	0.088	0.867	2.68	0.083	0.274	10.62	0.088
Asymmetry-α, %	18	24	16	0.083	0.920	1.52	0.233	0.435	20	0.559
F8-α SPD, μV²/Hz	54	54	31	0.106	0.713	7.04	0.003	0.278	42	1.20
P3-α SPD, μV²/Hz	394	276	147	0.078	0.968	0.58	0.567	0.056	237	1.32
P4-α SPD, μV²/Hz	411	264	144	0.094	0.810	4.10	0.025	0.057	288	1.32
Amplitude-θ, μV	8.7	9.6	7.4	0.083	0.916	1.60	0.216	0.066	7.75	0.376
Index-θ, %	12	21	4	0.110	0.692	7.81	0.002	0.287	14	2.17
Fp1-θ SPD, %	8.8	10.9	6.8	0.102	0.742	6.10	0.005	0.126	10.4	0.588
F3-θ SPD, μV²/Hz	60	51	29	0.097	0.782	4.88	0.013	0.064	40	1.10
F7-θ SPD, %	7.7	10.1	6.8	0.092	0.829	3.60	0.038	0.229	18.2	0.843
F8-θ SPD, μV²/Hz	31	29	14	0.101	0.753	5.75	0.007	0.159	20	1.32
T3-θ SPD, μV²/Hz	37	40	21	0.082	0.922	1.49	0.240	0.127	30	1.08
T3-θ SPD, %	9.8	10.3	6.2	0.081	0.939	1.14	0.331	0.126	10.3	0.466
T4-θ SPD, %	8.6	10.7	6.2	0.088	0.862	2.81	0.074	0.145	9.7	0.482
C4-θ SPD, %	10.1	11.6	8.6	0.088	0.862	2.80	0.074	0.048	11.1	0.422
P3-θ SPD, %	7.7	9.7	6.6	0.114	0.665	8.83	0.001	0.061	9.0	0.552
P3-θ SPD, μV²/Hz	45	52	27	0.088	0.858	2.89	0.069	0.093	42	0.888
P4-θ SPD, μV²/Hz	45	52	28	0.083	0.917	1.59	0.218	0.072	42	1.10
O2-θ SPD, μV²/Hz	27	45	30	0.108	0.703	7.39	0.002	0.199	30	0.884
P4-δ SPD, μV²/Hz	169	159	77	0.094	0.805	4.24	0.023	0.099	107	0.886
Amplitude mode, %	41.5	47.3	45.2	0.093	0.814	3.99	0.027	0.059	39.1	0.322
(VLF + ULF) SPD, %	45.3	54.5	50.8	0.136	0.557	13.92	0.000	0.108	58.6	0.276
HF SPD, ln msec²	5.60	4.87	5.00	0.112	0.679	8.26	0.001	0.052	5.85	0.083
LF/HF ratio	4.04	6.06	7.29	0.087	0.869	2.65	0.085	0.174	2.84	0.717
Mode HRV, msec	865	815	708	0.116	0.658	9.11	0.001	0.053	871	0.115
BSI, units	118	201	169	0.085	0.889	2.18	0.128	0.068	134	0.423
BARSI, units	2.18	3.02	4.12	0.098	0.773	5.15	0.011	0.359	1.50	0.500
KVI, units	–23	–17	6.5	0.080	0.952	0.88	0.425	0.105	–15	**15**
BP diastolic, mmHg	81.9	83.0	75.2	0.096	0.788	4.72	0.015	0.137	79.0	0.083
Triiodothyronine, nM/L	1.64	2.22	1.76	0.103	0.740	6.14	0.005	0.313	2.20	0.227
Aldosterone, pM/L	229	227	192	0.083	0.924	1.51	0.230	0.437	238	0.187
PAI	1.25	1.26	0.78	0.078	0.970	0.53	0.591	0.427	1.70	0.245
Variables currently not in the model	**> +2.5 %**	**± 2.5 %**	**< –2.5 %**	**Wilks' Λ**	**Partial Λ**	**F to enter**	**p-level**	**Tolerance**	**Reference**	**Cv**
(VLF + LF)/HF ratio	8.5	16.0	14.0	0.076	0.999	0.004	0.996	0.067	6.7	0.544
BP systolic, mmHg	137.3	134.7	118.1	0.073	0.966	0.593	0.558	0.352	124.5	0.122

Notes: step 35, N of vars in model: 35; grouping: 3 groups. Wilks' Λ: 0.076; approx. $F_{(70.7)} = 2.6$; $p < 10^{-5}$.

Table 11. Summary of stepwise analysis for predicting variables, ranked by criterion Λ

Variables currently in the model	F to enter	p-level	Λ	F-value	p-level
KVI, units	4.755	0.012	0.879	4.755	0.012
C3-β SPD, %	3.421	0.038	0.799	4.048	0.004
Triiodothyronine, nM/L	3.091	0.052	0.731	3.787	0.002
P4-α SPD, μV²/Hz	3.095	0.052	0.668	3.682	0.001
PAI, points	2.479	0.092	0.621	3.497	10^{-4}
T3-θ SPD, %	2.564	0.085	0.575	3.401	10^{-4}
BARSI, units	3.184	0.048	0.522	3.455	10^{-4}
T6-β SPD, μV²/Hz	2.303	0.108	0.486	3.366	10^{-4}
Frequency-α, Hz	2.290	0.110	0.452	3.302	10^{-4}
T4-θ SPD, %	1.869	0.163	0.426	3.197	10^{-4}
F3-θ SPD, μV²/Hz	1.908	0.157	0.400	3.120	10^{-4}
O2-θ SPD, μV²/Hz	1.928	0.155	0.375	3.061	10^{-4}
Index-θ, %	2.084	0.134	0.349	3.034	10^{-4}
Fp1-θ SPD, %	1.557	0.220	0.331	2.954	10^{-4}
P4-θ SPD, μV²/Hz	1.565	0.218	0.313	2.887	10^{-4}
P3-θ SPD, μV²/Hz	1.930	0.155	0.292	2.869	10^{-4}
LF/HF ratio	1.549	0.222	0.276	2.816	10^{-4}
F8-α SPD, μV²/Hz	1.702	0.192	0.259	2.787	10^{-4}
F8-θ SPD, μV²/Hz	1.308	0.279	0.246	2.723	10^{-4}
SPD (VLF + ULF), %	1.285	0.286	0.234	2.664	10^{-4}
Asymmetry-α, %	1.015	0.370	0.225	2.585	10^{-4}
P3-α SPD, μV²/Hz	1.766	0.182	0.210	2.583	10^{-4}
P3-θ SPD, %	1.412	0.254	0.198	2.552	10^{-4}
BSI, units	1.209	0.308	0.188	2.505	10^{-4}
SPD HF, ln msec²	2.965	0.062	0.166	2.618	10^{-4}
Amplitude mode, %	1.179	0.317	0.158	2.571	10^{-4}
Mode HRV, msec	1.023	0.368	0.150	2.514	10^{-4}
BP diastolic, mmHg	1.855	0.169	0.138	2.535	10^{-4}
F7-θ SPD, %	2.344	0.109	0.124	2.601	10^{-4}
C4-θ SPD, %	2.283	0.115	0.111	2.663	10^{-4}
P4-δ SPD, μV²/Hz	2.434	0.101	0.099	2.741	10^{-5}
F3-β SPD, %	1.230	0.304	0.093	2.708	10^{-5}
Amplitude-θ, μV	1.141	0.331	0.088	2.668	10^{-5}
T3-θ SPD, μV²/Hz	1.594	0.217	0.080	2.675	10^{-5}
Aldosterone, pM/L	1.029	0.368	0.076	2.628	10^{-4}

Table 12. Parameters of Wilks' statistics for predicting variables

Coefficients	Standardized		Raw	
Variables currently in the model	Root 1	Root 2	Root 1	Root 2
KVI, units	–0.714	–0.238	–0.035	–0.012
C3-β SPD, %	0.344	0.322	0.030	0.028
Triiodothyronine, nM/L	0.967	–0.329	0.727	–0.247
P4-α SPD, μV²/Hz	–1.957	0.516	–0.0048	0.0013
PAI, points	0.144	–0.302	0.275	–0.578
T3-θ SPD, %	–0.755	0.178	–0.167	0.039
BARSI, units	0.754	0.540	0.335	0.239
T6-β SPD, μV²/Hz	0.440	–0.861	0.0063	–0.0124
Frequency-α, Hz	–0.536	0.658	–0.508	0.623
T4-θ SPD, %	0.889	–0.726	0.155	–0.126
F3-θ SPD, μV²/Hz	–2.001	–0.431	–0.0337	–0.0073
O2-θ SPD, μV²/Hz	1.342	–0.128	0.028	–0.0026
Index-θ, %	1.033	–0.589	0.033	–0.019
Fp1-θ SPD, %	1.569	–0.211	0.226	–0.0304
P4-θ SPD, μV²/Hz	–0.345	1.355	–0.006	0.025
P3-θ SPD, μV²/Hz	1.355	–0.167	0.031	–0.0039
LF/HF ratio	0.828	0.578	0.163	0.114
F8-α SPD, μV²/Hz	1.103	–0.243	0.0169	–0.0037
F8-θ SPD, μV²/Hz	–1.376	–0.036	–0.0401	–0.0010
SPD (VLF + ULF), %	2.164	0.655	0.115	0.035
Asymmetry-α, %	0.164	–0.530	0.013	–0.041
P3-α SPD, μV²/Hz	–0.191	–0.965	–0.0005	–0.0024
P3-θ SPD, %	–2.488	–0.810	–0.443	–0.144
BSI, units	–0.228	–1.659	–0.0013	–0.0095
SPD HF, ln msec²	2.694	0.613	2.028	0.461
Amplitude mode, %	1.491	1.531	0.0946	0.0971
Mode HRV, msec	–2.722	–0.763	–0.0199	–0.0056
BP diastolic, mmHg	–1.333	–0.380	–0.1306	–0.0372
F7-θ SPD, %	–0.652	–0.829	–0.126	–0.160
C4-θ SPD, %	1.763	0.753	0.322	0.138
P4-δ SPD, μV²/Hz	–1.521	0.334	–0.0083	0.0018
F3-β SPD, %	–0.605	0.246	–0.045	0.018
Amplitude-θ, μV	1.227	0.229	0.264	0.049
T3-θ SPD, μV²/Hz	–0.785	0.438	–0.021	0.011
Aldosterone, pM/L	–0.114	–0.366	–0.0028	–0.0091
	Constants		7.481	–1.589
	Eigenvalues		4.615	1.345
	Canonical R		0.907	0.757
	Wilks' Λ		0.076	0.426
	χ^2		134	44
	Degree freedom		70	34
	p		10^{-5}	0.111
Cumulative proportions			0.774	1

Table 13. Correlations variables-canonical roots, means of roots and predicting variables Z-score

Change in variables	Correlations Variables-roots		EKI > +2.5 %	EKI ± 2.5 %	EKI < –2.5 %
Root 1 (77.4 %)	Root 1	Root 2	–3.66	0.93	2.83
KVI	0.121	0.228	–0.58 ± 0.39	–0.15 ± 0.20	1.48 ± 0.27
1/mode HRV	0.113	0.139	0.01 ± 0.34	0.57 ± 0.19	1.71 ± 0.24
BARSI	0.100	0.079	0.90 ± 0.68	2.03 ± 0.45	3.56 ± 0.80
F3-β SPD r	0.124	0.017	–0.81 ± 0.15	–0.21 ± 0.17	0.12 ± 0.48
C3-β SPD r	0.140	0.067	–0.65 ± 0.20	–0.04 ± 0.20	0.55 ± 0.23
HF SPD ln a	–0.102	0.073	–0.71 ± 0.51	–1.95 ± 0.36	–1.73 ± 0.88
HF/LF HRV	–0.090	0.018	–0.66 ± 0.34	–1.54 ± 0.37	–2.16 ± 1.23
P4-α SPD a	–0.086	–0.032	0.32 ± 0.34	–0.15 ± 0.24	–0.38 ± 0.14
P3-α SPD a	–0.075	–0.044	0.28 ± 0.31	–0.03 ± 0.15	–0.37 ± 0.12
F3-θ SPD a	–0.050	–0.070	0.46 ± 0.37	0.25 ± 0.19	–0.25 ± 0.11
BP systolic			0.84 ± 0.37	0.67 ± 0.17	–0.42 ± 0.20
P4-δ SPD a	–0.035	–0.094	0.66 ± 0.43	0.54 ± 0.30	–0.32 ± 0.26
F8-θ SPD a	–0.037	–0.092	0.40 ± 0.40	0.32 ± 0.17	–0.24 ± 0.15
Root 2 (22.6 %)	Root 1	Root 2	0.50	–0.60	3.44
Aldosterone	–0.038	–0.231	–0.21 ± 0.18	–0.24 ± 0.10	–1.05 ± 0.13
PAI	–0.045	–0.206	–1.09 ± 0.31	–1.06 ± 0.17	–2.21 ± 0.59
T3-θ SPD r	–0.026	–0.210	–0.11 ± 0.20	–0.01 ± 0.14	–0.86 ± 0.21
T4-θ SPD r	0.029	–0.209	–0.23 ± 0.24	0.22 ± 0.19	–0.75 ± 0.24
F7-θ SPD r	0.056	–0.184	–0.68 ± 0.06	–0.53 ± 0.05	–0.74 ± 0.09
Fp1-θ SPD r	0.029	–0.162	–0.27 ± 0.20	0.08 ± 0.18	–0.59 ± 0.19
C4-θ SPD r	0.025	–0.149	–0.22 ± 0.29	0.10 ± 0.17	–0.54 ± 0.27
P3-θ SPD r	0.039	–0.156	–0.26 ± 0.17	0.13 ± 0.18	–0.50 ± 0.19
P3-θ SPD a	–0.001	–0.144	0.08 ± 0.25	0.26 ± 0.18	–0.41 ± 0.18
P4-θ SPD a	0.002	–0.114	0.06 ± 0.19	0.21 ± 0.19	–0.31 ± 0.12
Index-θ	0.029	–0.150	–0.06 ± 0.20	0.26 ± 0.17	–0.32 ± 0.09
BSI	0.084	–0.086	–0.22 ± 0.25	0.96 ± 0.22	0.48 ± 0.82
BP diastolic	–0.020	–0.180	0.44 ± 0.42	0.61 ± 0.22	–0.58 ± 0.38
Amplitude-θ	0.012	–0.123	0.32 ± 0.32	0.62 ± 0.25	–0.13 ± 0.28
O2-θ SPD a	0.056	–0.103	–0.12 ± 0.18	0.55 ± 0.30	–0.01 ± 0.18
Amplitude mode	0.065	–0.064	0.16 ± 0.17	0.56 ± 0.19	0.38 ± 0.46
Triiodothyronine	0.082	–0.152	–1.11 ± 0.34	0.05 ± 0.25	–0.88 ± 0.56
Asymmetry-α	0.065	–0.186	–0.23 ± 0.20	0.35 ± 0.18	–0.37 ± 0.19
T3-θ SPD a	–0.013	–0.116	0.23 ± 0.29	0.30 ± 0.17	–0.28 ± 0.12
T6-β SPD a	0.085	–0.153	–0.30 ± 0.10	0.23 ± 0.16	–0.21 ± 0.14
F8-α SPD a	–0.018	–0.080	0.25 ± 0.23	0.26 ± 0.19	–0.21 ± 0.13
(VLF + ULF) SPD r	0.085	–0.089	–0.83 ± 0.25	–0.28 ± 0.17	–0.38 ± 0.32
(VLF + LF)/HF ratio			0.62 ± 0.35	2.43 ± 0.48	2.03 ± 0.94
Frequency-α	–0.034	0.135	0.03 ± 0.24	–0.31 ± 0.17	0.23 ± 0.18

Table 14. Squared Mahalanobis distances between predictors of change in EKI, F-values (df = 35.4) and p-levels

Clusters of change	EKI ± 2.5 %	EKI < –2.5 %	EKI > +2.5 %
EKI ± 2.5 %	0	20	22
EKI < –2.5 %	1.54 0.102	0	51
EKI > +2.5 %	4.07 10^{-4}	3.26 10^{-3}	0

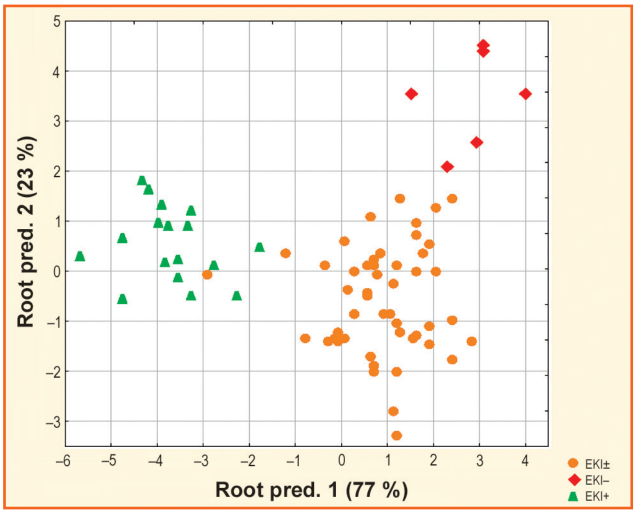

Figure 8. Individual values of discriminant roots of predicting parameters for different variants of changes in the electrokinetic index

Table 15. Coefficients and constants for classification functions for predictors of change in EKI

Clusters of changes	EKI ± 2.5 %	EKI < –2.5 %	EKI > +2.5 %
1	2	3	4
Variables currently in the model	p = 0.681	p = 0.083	p = 0.236
KVI, units	4.524	4.411	4.671
C3-β SPD, %	2.301	2.469	2.195
Triiodothyronine, nM/L	–17.73	–17.35	–21.34
P4-α SPD, μV²/Hz	0.175	0.171	0.198
PAI, points	13.50	11.69	11.60
T3-θ SPD, %	5.622	5.464	6.431
BARSI	–0.447	1.156	–1.720
T6-β SPD, μV²/Hz	–0.061	–0.099	–0.104
Frequency-α, Hz	38.48	40.03	41.50
T4-θ SPD, %	1.033	0.818	0.184
F3-θ SPD, μV²/Hz	–0.264	–0.357	–0.117
O2-θ SPD, μV²/Hz	–0.169	–0.127	–0.299
Index-θ, %	–1.073	–1.086	–1.245
Fp1-θ SPD, %	–5.608	–5.301	–6.680
P4-θ SPD, μV²/Hz	–0.419	–0.328	–0.361
P3-θ SPD, μV²/Hz	–0.160	–0.116	–0.308
LF/HF ratio	10.22	10.99	9.596
F8-α SPD, μV²/Hz	0.143	0.160	0.061
F8-θ SPD, μV²/Hz	–0.558	–0.638	–0.375
SPD (VLF + ULF), %	1.418	1.776	0.930
Asymmetry-α, %	–0.283	–0.424	–0.386
P3-α SPD, μV²/Hz	–0.097	–0.108	–0.098
P3-θ SPD, %	3.611	2.185	5.487
BSI, units	–0.073	–0.114	–0.078

End of Table 15

1	2	3	4
SPD HF, ln msec^2	42.64	48.36	33.84
Amplitude mode, %	2.471	3.042	2.143
Mode HRV, msec	0.769	0.708	0.854
BP diastolic, mmHg	8.095	7.697	8.654
F7-θ SPD, %	0.037	–0.850	0.440
C4-θ SPD, %	0.238	1.406	–1.089
P4-δ SPD, μV^2/Hz	0.271	0.263	0.311
F3-β SPD, %	–0.206	–0.217	0.021
Amplitude-θ, μV	5.341	6.042	4.185
T3-θ SPD, μV^2/Hz	0.202	0.210	0.310
Aldosterone, pM/L	0.134	0.092	0.137
Constants	–1099	–1102	–1142

Table 16. Regression summary for predictors of change in EKI

N = 72		Beta	St. err. of beta	B	St. err. of B	$t_{(64)}$	p-level
Variables	r		Intercept	–7.48	3.12	–2.40	0.019
Aldosterone, pM/L	0.32	0.304	0.106	0.028	0.010	2.86	0.006
T3 SPD entropy	0.22	0.239	0.112	4.301	2.006	2.14	0.036
Laterality-β, %	0.19	0.175	0.110	0.014	0.009	1.59	0.116
C3-δ SPD, %z	0.19	0.172	0.126	0.025	0.018	1.37	0.177
Popovych strain index	–0.24	–0.160	0.107	–4.062	2.729	–1.49	0.142
BARSI	–0.20	–0.141	0.109	–0.178	0.138	–1.29	0.201
F3-β SPD, %	–0.19	–0.186	0.120	–0.039	0.025	–1.56	0.124

Notes: *$R = 0.564$; $R^2 = 0.318$; adjusted $R^2 = 0.244$; $F_{(7.6)} = 4.3$; $p = 0.0006$; SE = 2.5 %.*

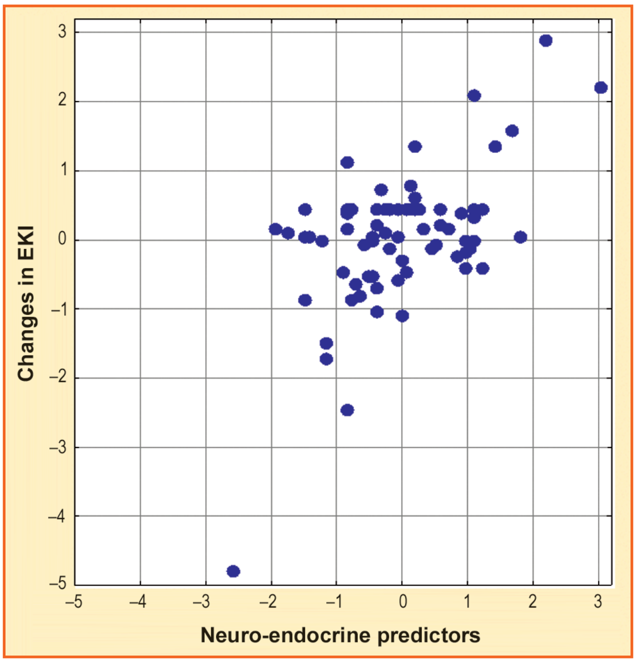

Figure 9. Scatterplot of canonical correlation between neuro-endocrine predictors (X-line) and changes in the electrokinetic index (Y-line)

Notes: *$R = 0.564$; $R^2 = 0.318$; $\chi^2_{(7)} = 25$; $p = 0.0006$; Λ prime = 0.682.*

Calculating individual classification functions by adding the products of their coefficients to the individual values of the predicting variables plus a constant (Table 15) allows us to predict a particular EKI response with an accuracy of 98.6 % (one error for a non-significant response).

At the same time, it turned out that using the regression model, it is possible to reliably predict not only the direction/quality of the EKI response to adaptogenic factors, but also its actual value (Table 16, Fig. 9). Interestingly, the standard error for estimation is the same 2.5 %, which we accepted as the range of insignificant reactions.

Discussion

Main findings

This study demonstrates for the first time that changes in the electrokinetic index of buccal epithelium in response to rehabilitation treatment are closely associated with a constellation of neuro-endocrine parameters, particularly EEG and HRV indices. Three key findings emerged from our analysis. First, EKI responses to adaptogenic factors are highly individualized and independent of both initial EKI levels and the specific nature of the intervention (electrostimulation, single balneofactor or their combination). Second, these individual responses can be predicted with high accuracy (98.6 %) using a multivariate model based on initial neuro-endocrine parameters. Third, changes in EKI correlate both linearly and nonlinearly with alterations in brain electrical activity, autonomic regulation, and aldosterone levels.

Interpretation in the context of existing knowledge

Our findings align with and extend previous research on cellular electrokinetic properties. Hughes [13] demonstrated that the ζ-potential of cells is mechanistically linked to membrane potential (Vm) and can dynamically change through ion channel activity, affecting cell-cell and cell-molecule interactions. Our observation that EKI correlates with EEG and HRV parameters suggests that systemic neuro-endocrine regulation may influence cellular electrokinetic properties through modulation of membrane potential. This hypothesis is supported by the strong association we found between EKI changes and aldosterone levels ($\beta = -0.219$, $p = 0.023$), as aldosterone is known to affect cellular ion transport and membrane polarization [47].

The age-related decline in EMN index reported by Czapla & McPhail [9] ($r = -0.71$ for men, $r = -0.60$ for women) may reflect cumulative changes in neuro-endocrine regulation over the lifespan. Our finding that EKI responses are determined by the initial constellation of neuro-endocrine variables, rather than by age per se, suggests that biological rather than chronological age is the key determinant of cellular electrokinetic properties.

Possible mechanisms

Several mechanisms may explain the observed neuro-endocrine correlates of EKI. First, autonomic nervous system activity, reflected in HRV parameters, may directly influence buccal epithelial cells through local neurotransmitter release. The oral mucosa is richly innervated by both sympathetic and parasympathetic fibers [15], and autonomic neurotransmitters can affect cellular membrane potential through receptor-mediated mechanisms. Our finding that VLF and LF bands of HRV correlate with EKI supports this pathway.

Second, cortical activity, particularly in frontal and temporal regions (cluster 1 in our analysis), may influence EKI through descending autonomic pathways. The strong correlation between beta-rhythm in F4 and T4 loci and EKI changes suggests that cortical regulation of autonomic tone may be a key mediator. This is consistent with the concept of "central autonomic network" described by Thayer & Lane [44], which links prefrontal cortical activity with peripheral autonomic regulation.

Third, hormonal factors, particularly aldosterone, may affect cellular electrokinetic properties through modulation of ion transport. Aldosterone regulates epithelial sodium channels (ENaC) and Na^+/K^+-ATPase activity [47], which directly influence cellular membrane potential and, consequently, ζ-potential. The inverse correlation we observed between aldosterone and EKI ($\beta = -0.219$) may reflect a compensatory mechanism: increased aldosterone secretion in response to stress may alter cellular ion balance, affecting electrokinetic properties.

The ambiguous responses of EKI to electrostimulation with the VEB device, revealed in this study, are realized not only through its various neuro-endocrine effects [24, 40], but also, probably, through a direct effect on the buccal epithelium, as was established by Shckorbatov et al. [48–50] in in vitro experiments using microwave radiation. It was shown that irradiation of cells induced a decrease in electric charge of native human buccal epithelium cell nuclei and an increase in chromatin condensation in nuclei. The observed effects depend on both irradiation dose and individual peculiarities of donors.

According to the concept of the Truskavetsian scientific school of balneology and phytotherapy [27, 42], the Naftussya bioactive water and ozokerite exert modulating neuro-endocrine (as well as immunotropic) effects by the aryl hydrocarbons present in their composition, which bind to the ubiquitous aryl hydrocarbon receptors of neurons, endocrinocytes and immunocytes. Therefore, the similarity of EKI responses to the three adaptogenic interventions is quite natural and was expected by us based on previous data [40]. Moreover, similarity of adaptogenic effects of Naftussya bioactive water and phytocomposition Balm Truskavets [41, 51, 52], which contains probable agonists of aryl hydrocarbon receptors [53], was revealed.

Clinical implications

Our findings have several potential clinical applications. First, the high predictive accuracy of our model (98.6 %) suggests that initial neuro-endocrine profiling could be used to personalize rehabilitation programs. Patients with specific neuro-endocrine patterns may benefit from tailored interventions targeting their individual regulatory mechanisms. Second, EKI monitoring during rehabilitation could serve as an integrative biomarker of treatment effectiveness, reflecting systemic neuro-endocrine changes. Third, the independence of EKI responses from the specific type of adaptogenic factor suggests that individual regulatory capacity, rather than treatment modality, is the primary determinant of outcomes. This supports a patient-centered approach to rehabilitation.

Comparison with other biomarkers

Compared to traditional biomarkers of adaptation (cortisol, heart rate variability, blood pressure), EKI offers several advantages. It is non-invasive, requires minimal equipment, and provides rapid results. Moreover, as our study demonstrates, EKI integrates information from multiple regulatory systems (neural, autonomic, endocrine), making it a potentially more comprehensive marker of adaptive capacity. However, further research is needed to establish its sensitivity and specificity compared to established biomarkers.

Strengths and limitations

The main strengths of this study include: 1) comprehensive assessment of multiple physiological systems; 2) large number of measured parameters allowing for robust multivariate analysis; 3) use of advanced statistical methods including regression, discriminant analysis, and cluster analysis; 4) high predictive accuracy of the developed models.

However, several limitations should be acknowledged. First, the study population was heterogeneous, including both healthy individuals and patients with chronic pyelonephritis in remission. While all participants showed signs of maladaptation, the underlying mechanisms may differ between these groups. Future studies should examine homogeneous populations to clarify these relationships. Second, the three treatment regimens differed in duration (4, 7, and 10–11 days) and modality. Although we found no significant differences in EKI responses between regimens, the study was not designed as a randomized controlled trial, limiting causal inferences. Third, we did not measure EKI at multiple time points during treatment, precluding analysis of temporal dynamics. Fourth, the mechanisms linking neuro-endocrine parameters to EKI remain speculative and require experimental validation. Fifth, we did not perform external validation of our predictive model on an independent sample, which is necessary before clinical application.

Future research directions

Several questions remain to be addressed in future studies. First, longitudinal studies with repeated EKI measurements are needed to characterize the temporal dynamics of changes and their relationship to treatment outcomes. Second, experimental studies manipulating specific neuro-endocrine parameters (e.g., through pharmacological interventions) could establish causal relationships. Third, investigation of cellular and molecular mechanisms linking systemic regulation to epithelial electrokinetic properties would provide mechanistic insights. Potential approaches include patch-clamp studies of ion channel activity in buccal epithelial cells under different autonomic and hormonal conditions. Fourth, validation of our predictive model in independent cohorts and different clinical populations is essential. Finally, comparative studies examining EKI alongside established biomarkers would help define its clinical utility.

Conclusions

This study demonstrates that electrokinetic index of buccal epithelium is closely associated with neuro-endocrine regulation, particularly brain electrical activity, autonomic tone, and aldosterone levels. Individual EKI responses to rehabilitation treatment are highly variable but can be accurately predicted from initial neuro-endocrine parameters. These findings suggest that EKI may serve as an integrative biomarker of adaptive capacity and could be useful for personalizing rehabilitation programs. Further research is needed to elucidate underlying mechanisms and validate clinical applications.

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Нейроендокринні кореляти та предиктори змін електрокінетичного індексу букального епітелію під час реабілітаційного лікування: багатовимірний аналіз

Резюме. ***Актуальність.*** Раніше ми показали, що кількісно-якісні кластери артеріального тиску дуже чітко відрізняються один від одного залежно від віку, статі пацієнтів та комплексу нейроендокринних, імунних й метаболічних змінних, який ми назвали тензіорегуломом. Тензіорегулом також включав електрокінетичний індекс (ЕКІ) букального епітелію, що формально не можна віднести ні до нейроендокринно-імунного, ні до метаболічного комплексу. ***Мета:*** визначити, як зміни ЕКІ корелюють зі змінами параметрів електричної активності мозку, варіабельності серцевого ритму (ВСР) та вмістом гормонів адаптації в осіб із дезадаптацією. ***Матеріали та методи.*** Під спостереженням перебували 42 чоловіки та 30 жінок без клінічного діагнозу або з хронічним пієлонефритом у фазі ремісії (23 чоловіки), але з відхиленнями в окремих показниках нейроендокринно-імунного комплексу як проявом дезадаптації. При надходженні на реабілітацію їм визначали ЕКІ, а також артеріальний тиск та нейроендокринні показники. Після трьох режимів реабілітаційного лікування із застосуванням різних адаптогенних факторів усі тести повторювали. ***Результати.*** Початковий ЕКІ знаходився в діапазоні 20 ÷ 71,4 %. Його зміни в межах 2,5 %, оцінені як несуттєві, зареєстровано в 49 випадках. Однак у 17 пацієнтів ЕКІ значуще підвищився, а у 6 — знизився. Реакція ЕКІ на застосування адаптогенних факторів не залежала від його початкового рівня. Ні спрямованість, ні величина відповідей ЕКІ, ні їх відсутність також не залежали від природи адаптогенних факторів. Спостерігалися як лінійні (прямі й обернені), так і нелінійні кореляції між змінами ЕКІ та 32 нейроендокринних показників. Для регресійної моделі було обрано 19 змінних: альдостерон; п'ять параметрів бета-, чотири альфа-, два дельта- та два тета-ритмів ЕЕГ, ентропію СЩП у локусі T3; три параметри ВСР, а також співвідношення систолічного артеріального тиску при першому і другому вимірюванні (BPS_2/BPS_1). Зміни цих показників пояснюють 72 % варіабельності змін ЕКІ. За результатами дискримінантного аналізу, розпізнавальними стосовно характеру реакції ЕКІ виявилися зміни 24 показників. З іншого боку, визначено 35 вихідних показників як предикторів індивідуальних реакцій ЕКІ (точність класифікації 98,6 %). Виявилося також, що за допомогою регресійної моделі можна надійно передбачити не лише направленість (якість) індивідуальної реакції ЕКІ, але і її фактичну величину (стандартна похибка для оцінки становить 2,5 %). ***Висновки.*** Реакції електрокінетичного індексу на адаптогенні фактори є неоднозначними і корелюють лінійно (прямо й обернено) та нелінійно зі змінами показників ЕЕГ і ВСР, а також рівнями альдостерону в осіб із дезадаптацією. Якість та величина відповіді ЕКІ не залежать від його початкового рівня або природи адаптогенних факторів, але можуть бути надійно передбачені (точність 98,6 %) за допомогою 35 початкових нейроендокринних показників: 23 — ЕЕГ, 7 — ВСР, рівнів трийодтироніну, альдостерону і діастолічного артеріального тиску, а також вегетативного індексу Кердо й індексу адаптації Поповича. Ці результати свідчать про те, що ЕКІ може слугувати інтегративним біомаркером нейроендокринної регуляції та бути корисним у плануванні персоналізованої програми реабілітації.

Ключові слова: електрокінетичний індекс букального епітелію; електроенцефалографія; варіабельність серцевого ритму; гормони адаптації; багатовимірний аналіз