Selected neuroendocrine factors as potential molecular biomarkers of early non-affective psychosis course in relation to treatment outcome: A pilot study

Marie Obdržálková [a,1], Libor Ustohal [a,c,*,1], Nataša Hlaváčová [b], Michaela Mayerová [a], Eva Češková [a], Tomáš Kašpárek [a], Daniela Ježová [b]

[a] Department of Psychiatry, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic
[b] Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia
[c] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Masaryk University, Brno, Czech Republic

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ABSTRACT

The aim of this pilot study was to find whether the dysregulation of neuroendocrine biomarker signaling pathways in the first episode of non-affective psychosis is a predictive factor of treatment outcome. Patients with the first episode of non-affective psychosis (N = 29) were examined at admission, at discharge, and at follow-up (N = 23). The biomarkers included serum aldosterone, cortisol, free thyroxine, thyroid stimulating hormone, and prolactin. We revealed lower baseline aldosterone and higher baseline cortisol concentrations in patients with very good outcome compared to those with good outcome after one year. We failed to reveal any significant association between treatment outcome and neurohumoral biomarkers in the whole sample at 1-year follow-up. However, baseline aldosterone concentrations negatively correlated with total PANSS scores at the discharge. Lower baseline aldosterone and higher baseline cortisol concentrations have the potential to predict a more favorable outcome for patients with the first episode of psychosis.

1. Introduction

Despite intensive research in the field of mental disorders (including schizophrenia), there are still significant gaps in the knowledge of etiologic factors and optimal treatment possibilities [1,2]. In this respect, relatively little attention has been given to endocrine regulatory factors in schizophrenia. It is surprising, as several hormones acting in the brain are known to induce molecular changes related to neurotransmitter actions and brain plasticity [3]. Of particular importance is to study patients with the first episode of psychosis which allows avoiding the possible confounding effects of chronic illness and allows a better understanding of biological abnormalities. We focused on the joint examination of endocrine regulatory factors, namely cortisol, prolactin, thyroid hormones, and aldosterone, which have a strong association with the pathophysiology or treatment of mental disorders.

The most frequently investigated hormonal system in patients with schizophrenia is the hypothalamic-pituitary-adrenocortical

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* Corresponding author. Department of Psychiatry, University Hospital Brno and Faculty of Medicine, Masaryk University, Jihlavská 20, 62500 Brno, Czech Republic.
E-mail address: ustohal.libor@fnbrno.cz (L. Ustohal).
[1] Shared first authorship.

(HPA) axis [4–6]. The executive limb of this axis is the glucocorticoid hormone cortisol and glucocorticoid hormones control a number of molecular signaling cascades underlying the physiological functioning of the body and the brain. It is known that exposure to inadequately high cortisol concentrations can induce undesirable effects, particularly in the brain, such as degenerative processes affecting neurons in the hippocampus and prefrontal cortex, altering the function of dopamine and other neurotransmitters related to schizophrenia [6]. Moreover, the HPA axis is one of the main neuroendocrine systems involved in the stress response [7]. Nevertheless, the results of studies on the HPA axis function in schizophrenia, including the first episode, are inconsistent [4,6].

Another mechanism that may, if dysregulated, lead to disturbances in mental functions, is the activation of brain mineralocorticoid receptors (MR). It is known for a long time that the main ligands of brain MR are glucocorticoids [8]. More recent studies bring evidence that the mineralocorticoid hormone aldosterone is able to bind to MR in some brain regions with pathological consequences on mental health [9,10]. Aldosterone represents the executive end of the renin-angiotensin-aldosterone system (RAAS). The information on putative changes in aldosterone secretion in patients with schizophrenia is scarce [11].

The actions of several pituitary hormones and/or the regulatory mechanisms of their secretion overlap with the signaling pathways involved in the pathogenesis of mental disorders. With respect to the hypothalamic-pituitary-thyroid axis and schizophrenia, thyroid-stimulating hormone (TSH) concentrations are differently affected depending on the duration of the illness. In male patients with the first episode of schizophrenia, lower TSH, but no alterations in cortisol or prolactin concentrations were observed. On the other hand, higher cortisolemia was described in female patients compared to healthy controls [12]. Lower free thyroxine (fT4) concentrations have been associated with poorer cognitive functioning in patients with the first episode of psychosis [13,14]. However, the results of an older study showed reduced triiodothyronine (T3) not only in the first episode but also in drug-treated patients in the later stages of schizophrenia in comparison with healthy subjects [15]. Conversely, high prolactin concentrations were negatively associated with poorer cognitive performance in processing speed [16]. Moreover, it is generally known that increased prolactin release is a consequence of the blockade of D2 dopamine receptors by antipsychotic drugs with D2 antagonist properties [17].

It is hypothesized that dysregulation of neuroendocrine biomarker signaling pathways reflected by altered hormone concentrations at the time of the first episode of schizophrenia is a predictive factor of future treatment outcome. In this proof-of-concept study on a relatively small number of patients, we have decided to validate two approaches for future testing of this hypothesis and we have selected neuroendocrine markers, which received less attention in the previous research. The first approach is to make correlational analyses between neuroendocrine biomarkers at the time of admission to the hospital for the first episode of non-affective psychosis and the treatment outcome at a one-year follow-up. The second approach is a comparison of the concentrations of neuroendocrine biomarkers in blood at the time of admission to the hospital between the patients with good and those with very good outcomes at one-year follow-up. Our original objective was to compare patients with poor and good outcomes but due to an overall good response in the first-episode sample, we finally decided to assess differences between those with good and very good outcomes.

2. Methods

2.1. Subjects

The study sample consisted of patients admitted with the first episode of non-affective psychosis to the Department of Psychiatry of the Faculty of Medicine of Masaryk University and University Hospital Brno, Czech Republic from December 5, 2016, to August 23, 2019. Patients were included in the study if they met the following inclusion criteria: (1) diagnosis of schizophrenia (F20), acute psychosis with symptoms of schizophrenia (F23.1), or acute schizophreniform psychosis (F23.2) according to the International Classification of Diseases, revision 10 (ICD-10); (2) experiencing their first episode of psychosis; (3) no prior treatment with antipsychotic medication; and (4) absence of other psychiatric comorbidities, including organic and mood disorders, or substance abuse (excluded by urine toxicology tests) except for tobacco. The assessment of psychiatric diagnosis was conducted using the Mini International Neuropsychiatric Interview (MINI) [18]. All patients were examined by two independent experienced psychiatrists who had to confirm the diagnosis (it was done by authors MO, LU, or MM). The exclusion criteria were: (1) clinically relevant neurological or endocrine disease; (2) previous hospitalization for psychosis, and (3) involuntary hospitalization. Patients who met the inclusion criteria were offered participation in the study. All aspects related to the study were explained to them by members of the team and they were made familiar with the informed consent for the study. Any questions they had were answered. Out of 34 patients of both sexes who met the study criteria, 29 patients (9 males, 20 females) with a mean age of 27.03 ± 1.1 years agreed to participate. All subjects signed informed consent. The study was approved by the local ethics committee of the University Hospital Brno, Czech Republic, and complies with the requirements of the Declaration of Helsinki.

2.2. Study procedures

Patients were examined at the time of admission to the hospital or the next workday (baseline), at the discharge from the hospital (discharge), and at follow-up one year after the admission to the hospital (follow-up). The follow-up examination was performed during a voluntary 3-day hospitalization. At each time point, a detailed psychiatric evaluation and a collection of blood samples for biomarker measurements were completed. Samples for the measurement of serum hormone concentrations (including cortisol) were taken after at least 8 h of bed rest, immediately after awakening (around 6 a.m.). Blood sampling was done the second workday after the admission of patients so their exposure to antipsychotics was shorter than three days. They took only one or two doses of antipsychotics (including titration) before blood sampling.

2.3. Clinical rating scales

The severity of psychopathology was evaluated by the Positive and Negative Syndrome Scale (PANSS) [19] and Clinical Global Impression (CGI) at every visit. The PANSS has three subscales including a seven-item positive (PANSS-P), a seven-item negative (PANSS-N), and sixteen-item general psychopathology (PANSS-G) subscale for a total of thirty items. The PANSS total (PANSS-T) score is computed by taking the sum of all thirty items. The duration of untreated psychosis (DUP) was measured as the time in weeks from the first positive psychotic symptoms to the start of the first adequate treatment of psychosis. The rater was the author MO (except for one patient who was rated by the author LU). All scales and interviews were done by the rater(s). The raters underwent meetings to ensure their reliability.

2.4. Biomarker measurements

Blood for biomarker measurements was collected from patients in supine position immediately after awakening. After centrifugation of blood at 4 °C, the aliquots of serum were stored at −18 °C until analyzed. Concentrations of serum aldosterone, cortisol and prolactin concentrations were measured in samples collected from all time points. In addition, free thyroid hormone (fT4) and thyroid-stimulating hormone (TSH) concentrations were analyzed from samples collected at baseline and follow-up. Serum aldosterone concentrations were measured using radioimmunoassay with a commercial kit (RIA, Aldosterone, Beckman Coulter, Prague, Czech Republic). Serum cortisol concentrations were measured using a chemiluminescent microparticle immunoassay (CMIA, Abbott Architect, USA). Serum prolactin concentrations were measured using a chemiluminescent microparticle immunoassay (CMIA, Abbott Architec, USA). Serum TSH and fT4 concentrations were measured using an electrochemiluminescent immunoassay (Roche Diagnostic, Germany). The samples were analyzed in the certified labs of the University Hospital Brno, Czech Republic.

2.5. Statistics

The values were checked for the normality of distribution using the Shapiro-Wilks test. The statistical analysis of data was performed by paired or unpaired Student's t-test as well as repeated measure one-way ANOVA with Greenhouse-Geisser correction as appropriate. In the case of repeated measure one-way ANOVA, multiple comparisons by Tukey test were performed. We calculated a percentage of reduction in the PANSS total score change from baseline to one-year follow-up assessment, with the reduction in score indicating an improvement in symptoms. The atypical antipsychotics and their doses were converted into chlorpromazine equivalents according to Woods [20].

Pearson's correlation was computed to determine relationships between hormone concentrations and scores in PANSS. Values are expressed as means ± standard deviations (SD). The overall level of statistical significance was defined as $p < 0.05$.

Table 1
Baseline demographic and clinical characteristics of patients (n = 23).

Characteristics	Mean ± SD
Age (years)	26.5 ± 5.5
	18/36 (min/max)
BMI	23.4 ± 4.9
	15.7/37.2 (min/max)
Duration of untreated psychosis (weeks)	10.4 ± 11.6
	1/37 (min/max)
CGI-S (score)	5.3 ± 0.81
	3/6 (min/max)
PANSS: Positive scale (score)	28.1 ± 6.6
	18/40 (min/max)
Negative scale (score)	29.4 ± 9.5
	7/41 (min/max)
General psychopathology scale (score)	55.3 ± 13.4
	19/76 (min/max)
Total (score)	112.9 ± 26.5
	46/151 (min/max)
	(n/%)
Sex: men women	6/26.1
	17/73.9
Antipsychotic-naive	23/100
ICD-10 Diagnosis: F20.0	5/21.7
F20.3	4/17.4
F23.1	13/56.5
F23.2	1/4.3

BMI – Body Mass Index; CGI-S -Clinical Global Impression – Severity scale; F20.0 - Paranoid schizophrenia; F20.3 - Undifferentiated schizophrenia; F23.1 - Acute polymorphic psychotic disorder with symptoms of schizophrenia; F23.2 - Acute schizophrenia-like psychotic disorder; PANSS – Positive and Negative Syndrome Scale.
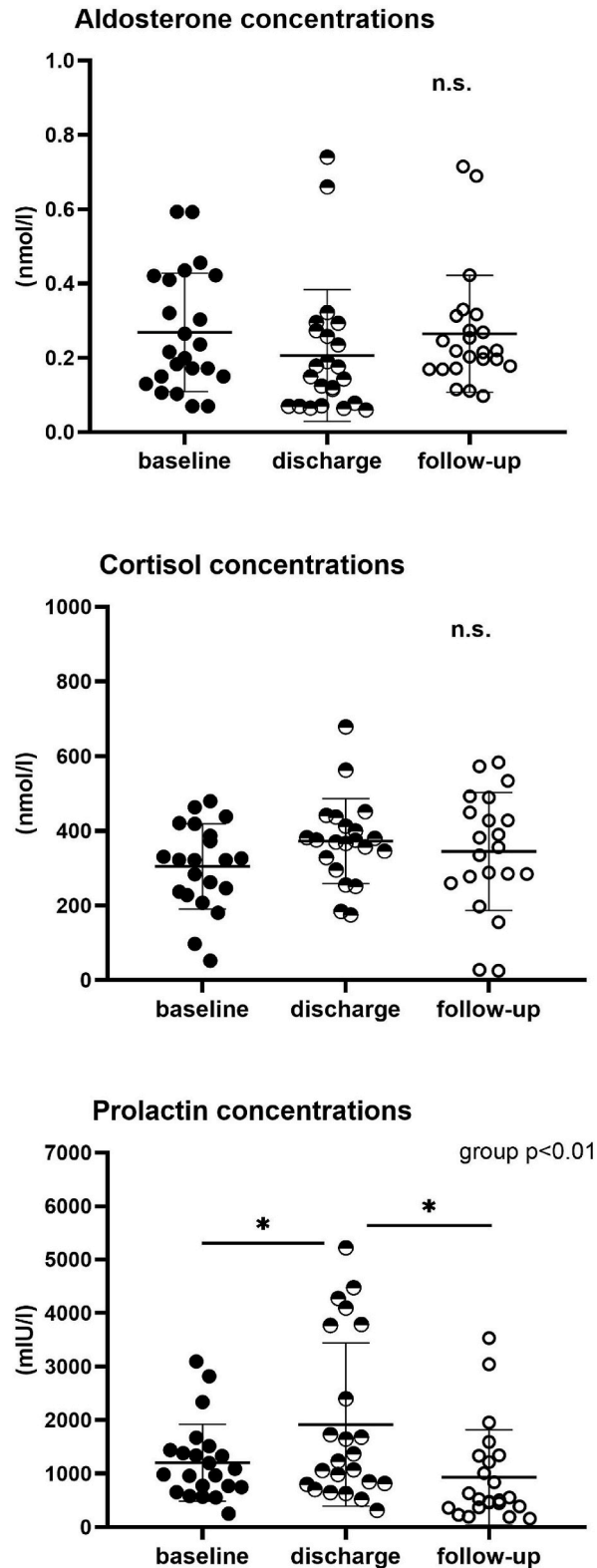
Fig. 1. Serum concentrations of aldosterone, cortisol and prolactin at the baseline, discharge, and one-year follow-up measurements in patients with the first episode of non-affective psychosis (n = 23). Results are expressed as means ± SD. Statistical analysis by one-way ANOVA with subsequent Tukey post hoc test: *p < 0.05.

3. Results

Twenty-three patients completed one-year follow-up examinations (13 with the diagnosis F23.1, 1 with the diagnosis F23.2 and 9 with the diagnosis F20). Six patients missed the follow-up visit, out of them 4 refused to come, and 2 were unattainable (4 with the diagnosis F23.1 and 2 with the diagnosis F20). These 6 patients were outpatients and were stabilized according to the report of their psychiatrists. Baseline clinical and socio-demographic data are shown in Table 1. The median hospitalization duration was 41 days, the mean time was 41.3 days for all 29 patients, and the median hospitalization duration in 23 patients with follow-up visit was 42 days, the mean time was 41.3 days. At the time of hospital admission, all patients were antipsychotic-naïve. At the time of hospital discharge, 10 patients were taking olanzapine, 11 were taking risperidone, 1 was taking quetiapine and 1 was taking clozapine. At the time of the one-year follow-up, 4 patients were taking olanzapine, 5 were taking risperidone or paliperidone, 9 were taking aripiprazole, 1 was taking cariprazine, 2 were taking quetiapine and 2 were without antipsychotic treatment.

One-way ANOVA for repeated measures followed by multiple comparisons did not reveal differences in serum aldosterone and cortisol concentrations (Fig. 1) measured at the time of admission, discharge, and one-year follow-up. Serum prolactin concentrations
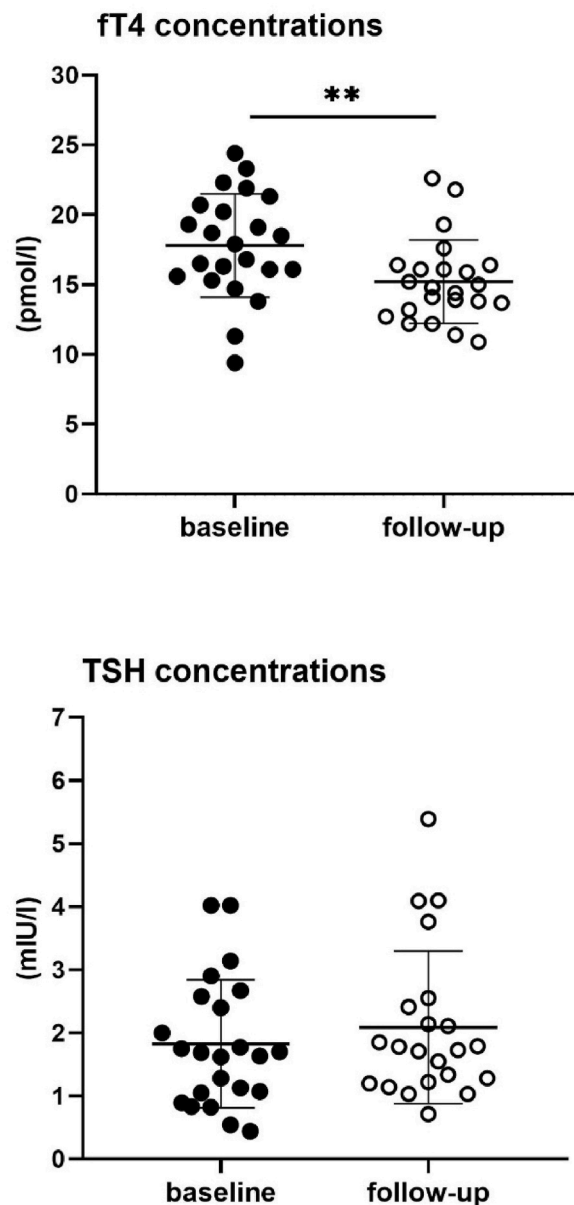

Fig. 2. Serum concentrations of fT4 and TSH at the baseline and one-year follow-up measurements in patients with the first episode of non-affective psychosis (n = 23). Results are expressed as means ± SD. Statistical analysis by paired *t*-test: **p < 0.01.

Improvement of PANSS total

Aldosterone concentrations
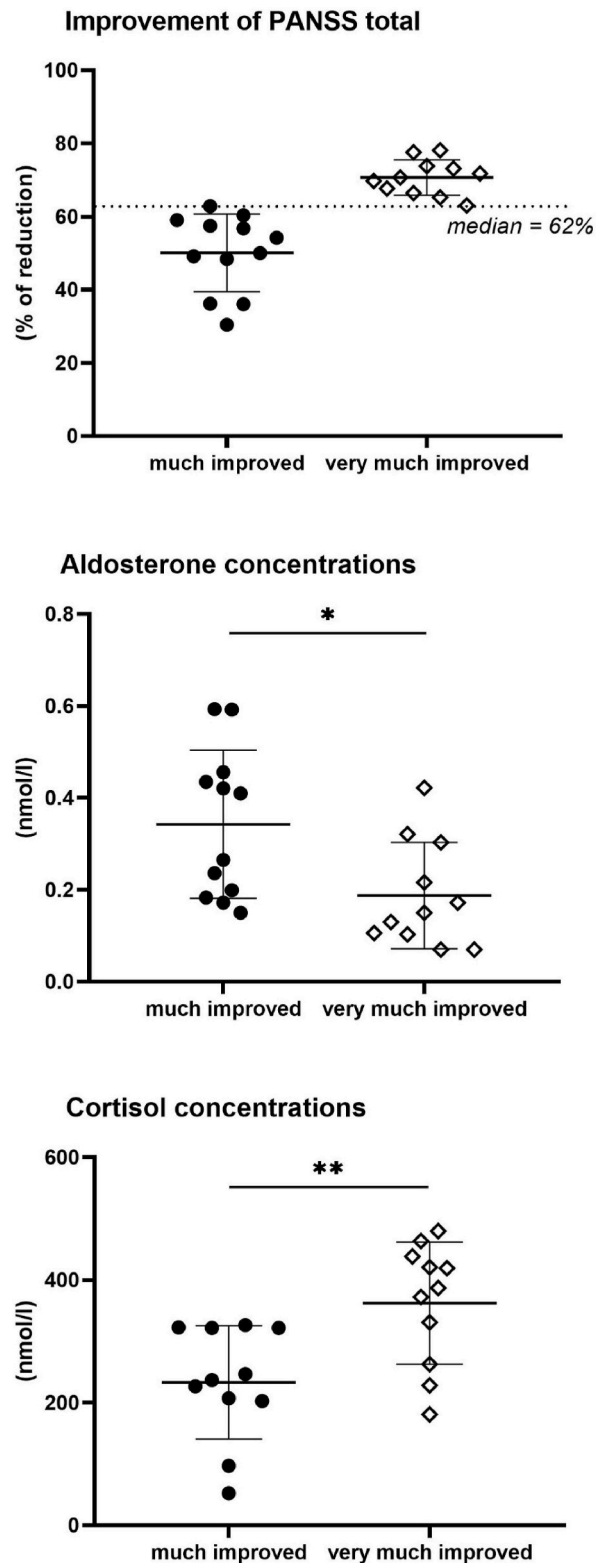

Cortisol concentrations

Fig. 3. Improvement of PANSS total score, serum aldosterone and cortisol concentrations in two patients' subgroups according to their treatment outcomes. The sample of patients was divided according to the median split of percentage reduction in total PANSS score from baseline (admission to the hospital) to one-year follow-up. First-episode psychosis patients were divided into two groups, those with much improvement in total PANSS (n = 12, reduction ≤62) and those with very much improvement in total PANSS score n = 11, reduction >63).

significantly changed over time ($F_{(1.44, 31.64)} = 7.116$, $p < 0.01$). Multiple comparisons by the Tukey post hoc test revealed that serum prolactin concentrations (Fig. 1) were significantly higher at the time of discharge compared to those at the baseline ($p < 0.05$) and follow-up measurements ($p < 0.05$). At the time of hospital discharge, there was no significant difference between serum prolactin concentrations between patients treated with olanzapine (n = 10) and risperidone (n = 11). When the antipsychotic type and dosage were converted into chlorpromazine equivalents, the correlation analysis showed a positive relationship between prolactin concentrations and chlorpromazine equivalents (r = 0.461; p = 0.04).

For technical reasons, concentrations of fT4 and TSH were not available at the time of hospital discharge. As revealed by paired *t*-test, serum concentrations of fT4 (Fig. 2) were significantly lower at the time of follow-up compared to those at the baseline ($t_{22} = 3.24$, $p < 0.01$). Serum TSH concentrations were similar at baseline and at the time of one-year follow-up (Fig. 2).

The correlation analyses between concentrations of neuroendocrine biomarkers at the baseline and scores in total PANSS as well as individual PANSS sub-scales at one-year follow-up failed to reveal any significant correlations. There was a negative correlation between baseline aldosterone concentrations and total PANSS scores at the discharge (r = −0.49, p < 0.05).

All participants achieved a clinically significant response (≥30 % reduction from baseline in PANSS total score) [21–23] by one-year follow-up. The poor outcome was defined as less than a 30 % reduction from baseline in PANSS total score at one-year follow-up. Only 2 patients were non-remitters, the rest of our sample reached the criteria for remission [24]. Our original objective was to compare patients with poor and good outcomes but due to an overall good response in our sample, we decided to assess differences between those with good and very good outcomes. The sample of patients was divided according to the median split of percentage reduction in total PANSS score from baseline (admission to the hospital) to one-year follow-up (Fig. 3). The median split of reduction was determined as 62 %. Thus, the sample was divided into two groups (good and very good outcomes), those with much improvement in total PANSS (n = 12, reduction ≤62) and those with very much improvement in total PANSS score (n = 11, reduction >63). As shown in Table S1, there was an equal diagnostic and sex distribution among the groups. Statistical analysis showed that baseline serum aldosterone concentrations (Fig. 3) at the time of admission were significantly higher in patients with much improvement in PANSS total score compared to those with very much improvement ($t_{21} = -3.12$, p < 0.01). The group of patients with much improved PANSS total score after one-year follow-up exhibited significantly lower baseline serum cortisol concentrations (Fig. 3) in comparison with the group of patients with very much improved PANSS total score ($t20 = 2.59$, p < 0.05). No differences between the groups were found in baseline serum prolactin, fT4, and TSH concentrations. The demographic and clinical characteristics of patients with good and very good outcomes are shown in Table S1.

4. Discussion

The results of the present study are in support of a potential role of adrenocortical steroids at the time of the first episode of non-affective psychosis as a predictor of one-year treatment outcome. In addition, a significant increase in serum prolactin concentrations has been observed at the time of hospital discharge compared to both hospital admission and one-year follow-up. Concentrations of fT4 decreased significantly at the time of the one-year follow-up.

The most intriguing results of the present study are the observation of lower baseline aldosterone and higher baseline cortisol concentrations in patients with very good outcome compared to those with good outcome at the time of one-year follow-up. Many previous studies have evaluated plasma or salivary cortisol concentrations under various conditions in antipsychotic-naïve patients with the first episode of psychosis in comparison with healthy subjects [4]. Findings from these studies support the presence of HPA axis hyperactivity and a blunted HPA axis response to stress at the onset of psychosis [4]. However, there are almost no studies on the changes in cortisol concentrations over longer follow-up periods as concluded in a recent paper by Allott et al. [25]. There is, however, a short-term follow-up study in the first episode of psychosis at baseline and response to antipsychotic treatment after 12 weeks [26]. The present data of higher baseline cortisol concentrations in patients with very good outcome compared to those with good outcome at the time of one-year follow-up are consistent with signs of lower HPA activity in treatment non-responders in the mentioned study. Thus, high baseline cortisol concentration might be one of the biomarkers predicting a favorable treatment outcome. An opposite prediction can be suggested for aldosterone concentration, as shown by low baseline aldosterone concentrations in patients with very good treatment outcome at one-year follow-up. This represents an original finding, which is however of little clinical value before verification on larger patient groups, including investigation of potential sex differences. The mechanism potentially underlying the association between baseline aldosterone and cortisol levels and clinical outcomes can include altered balance in central neurotransmitters and other supra-hypothalamic regulatory factors. It is known for a long time that the HPA axis is under the control of brain monoamines [27,28] and the balance between various regulatory molecules can influence both hormone concentrations and treatment outcomes.

The performance of correlation analyses, although they were considered as our first approach, failed to reveal any significant association between the one-year treatment outcome and any of the individual neurohumoral biomarkers. Concretely, there were no relationships between baseline hormone concentrations at the time of hospital admission and total PANSS as well as individual PANSS sub-scales at one-year follow-up. However, baseline aldosterone concentrations negatively correlated with total PANSS scores at the discharge. This finding is consistent with our previous observation of a negative correlation between aldosterone concentrations and clinical symptoms in patients with the first episode of schizophrenia [11].

The present finding of increased prolactin concentrations at the time of hospital discharge compared to those at hospital admission is not surprising. All patients with the first episode of psychosis included in the study were antipsychotic-naïve and antipsychotic treatment is well known to induce increased prolactin secretion. Elevated prolactin levels are mainly the result of the blockade of D2 dopamine receptors by antipsychotic drugs [17]. Accordingly, olanzapine treatment was found to induce a moderate, while

risperidone treatment strong increase in prolactin concentrations [29]. In the present study, the stratification of patients according to antipsychotic medication (olanzapine vs risperidone) at the time of hospital discharge failed to reveal any differences in prolactin concentration. In our sample, the dosage of the antipsychotic drugs seems to be of more importance. The medication used expressed in chlorpromazine equivalents positively correlated with concentrations of prolactin in serum, i.e. higher dosage of antipsychotics was associated with higher prolactin secretion. Interestingly, prolactin concentration returned back to the baseline at the time of the one-year follow-up. It is likely to be the consequence of different antipsychotic medications – most patients (n = 12) were treated with dopamine D2/D3 receptor partial agonists (aripiprazole or cariprazine) or were without antipsychotic medication. As prolactin is a stress hormone known to be increased under psychosocial stress situations [30], potential patients' better coping with real-life stress after successful treatment could have contributed to the lowering of hyperprolactinemia.

The decrease in serum fT4 at the time of one-year follow-up in comparison with the baseline is an original finding, which has not been published so far. Although a number of thyroid abnormalities were documented in chronic patients with schizophrenia [16], reports on direct comparison of fT4 levels before and after a successful treatment are scarce. Antipsychotic medication resulted in a decrease in fT4 and an increase in TSH concentration after recovery from acute psychosis at the time of hospital discharge [31]. Two previous studies in children and adolescents showed a decline in total thyroxine or fT4 with 3- or 6-month follow-ups [32,33]. The majority of participants in the mentioned studies were drug-naïve at the onset of the investigation and the thyroid hormones were affected mainly by the treatment with quetiapine. Consistently, the present study demonstrates attenuation of fT4 concentration after a longer time period of schizophrenia treatment, though without changes at the TSH level.

The strengths of this study are its longitudinal design and the fact that all patients were drug-naïve at the admission to hospital. The exposure to antipsychotics before the first blood sampling was very short.

The main limitation of the present study is the small sample size, therefore it can be considered only a pilot study. Moreover, the hypothesis has been formulated in a way that the possibility of type 1 error is very likely, so our results require cautious interpretation. Another limitation is an unequal number of male and female participants, which may implicate the results obtained. Further, the results on treatment outcomes pertain only to patients with good or very good outcomes, while those with poor outcomes are missing. That can be explained by the exclusion criteria – all patients had to be able to sign informed consent at the time of hospital admission (involuntarily hospitalized patients were excluded). Patients with alcohol and other substance abuse were not eligible for the study. Due to these exclusion criteria, more women than men were recruited and the patients had good treatment outcomes.

In conclusion, we have obtained only partial support for the hypothesis that a dysregulation of neuroendocrine biomarker signaling pathways reflected by altered hormone concentrations at the time of the first episode of psychosis is a predictive factor of future treatment outcomes. Lower baseline aldosterone and higher baseline cortisol concentrations have the potential to predict a favorable outcome for patients with the first episode of psychosis. Future testing of this hypothesis on a larger sample of subjects is however needed.

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Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Marie Obdržálková: Writing – original draft, Project administration, Investigation. **Libor Ustohal:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Nataša Hlaváčová:** Writing – original draft, Formal analysis, Data curation. **Michaela Mayerová:** Project administration, Investigation. **Eva Češková:** Supervision, Conceptualization. **Tomáš Kašpárek:** Supervision, Funding acquisition, Conceptualization. **Daniela Ježová:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21173.

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