Neuro- and immunomodulatory steroids and other biochemical markers in drug-naive schizophrenia patients and the effect of treatment with atypical antipsychotics

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Submitted: 2011-03-07 Accepted: 2011-03-20 Published online: 2011-04-29

Key words: **adrenal; steroids; biochemical parameters; schizophrenia; antipsychotics**

Neuroendocrinol Lett 2011; **32**(2):141–147 **PMID:** 21552193 NEL320211A01

Abstract

OBJECTIVE: Serum levels of neuro- and immunomodulatory adrenal steroids together with selected hormonal, lipid and other relevant biochemical parameters were investigated to examine the differences between first-episode schizophrenia patients and age-matched healthy subjects, and the effect of treatment with atypical antipsychotics.

METHODS: The patient´s group consisted of 22 drug-naive patients (13 men and 9 women), diagnosed with schizophrenia according to ICD-10 criteria, before and after six-months treatment with atypical antipsychotics of olanzapine or non-olanzapine type. Biochemical markers included steroids cortisol, dehydroepiandrosterone, its sulfate, 7-hydroxylated metabolites of dehydroepiandrosterone, prolactin, thyrotropin, free thyroxine, autoantibodies against thyroid peroxidase and thyroglobulin, glucose levels, four major lipid parameters, homocysteine and three other aminothiols. Steroids, prolactin and thyroid parameters were determined by radioimmunoassays, the other markers by standard biochemical methods.

RESULTS: Significantly lower dehydroepiandrosterone sulfate and of 7α-hydroxy-dehydroepiandrosterone levels than in controls were found in male patients. In the female group, the only difference in steroid spectra was significantly higher cortisolemia in the patients. The patients had also higher titres of autoantibodies against thyroid peroxidase. Compared to controls, the patients displayed worse lipid spectra, and higher homocysteinemia. Medication did not lead to significant changes in the parameters, with the exception of expected increase in prolactin levels in non-olanzapine treated subgroups.

CONCLUSION: Lower levels of 7α-hydroxydehydroepiandrosterone, abundant especially in brain, determined for the first time in schizophrenia patients, are in agreement with recent opinion of their neuroprotective and immunoprotective role. High levels of autoantibodies against thyroid peroxidase in the patients support the autoimmunity hypothesis of schizophrenia.

ORIGINAL ARTICLE

INTRODUCTION

Schizophrenia is associated with multiple functional system impairments, including hormonal imbalances on all hormonal axes (Taylor *et al.* 2009). Of particular importance are hormones involved in the hypothalamic-pituitary-adrenal (HPA) stress-neuroendocrine axis (Gispen-de Wied 2000; Hucklebridge *et al.* 2005; Quinones & Kaddurah-Daouk 2009). Cortisol, a major steroid stress hormone and the end product of the HPA axis, is one of the most studied hormones associated with psychiatric disorders, including schizophrenia. Because of its multiple effects on the immune system, e.g. on cytokine composition and the differentiation of Th1/Th2 lymphocytes, cortisol is a well-known immunomodulatory agent, that provides a link between the neuroendocrine and immune systems (Purohit & Reed 2002; Hucklebridge *et al.* 2005). In addition to impairment of its periodicity and lack of response to dexamethasone suppression, hypercortisolemia has been repeatedly reported in psychiatric patients (for review see Gispen-de Wied 2000; Hucklebridge *et al.* 2005; MacKenzie *et al.* 2007)

In the past decade, increasing evidence suggests that another adrenal steroid, dehydroepiandrosterone (DHEA), can mitigate some of the excessive effects of glucocorticoids, including those observed in the brain (Kalimi *et al.* 1994; Gallagher *et al.* 2008). DHEA can thus act as an endogenous anti-glucocorticoid. DHEA and its sulfate (DHEAS), its precursor pregnenolone sulfate, as well as progesterone and its saturated metabolites are neuroactive steroids. They may either positively or negatively modulate brain function through interaction with a number of ligand-gated ion channel associated receptors. For example, DHEA/S interacts with γ-aminobutyric acid Type A ($GABA_A$-R) and N-methyl-D-aspartate (NMDA) receptors (for review see Strous 2005; MacKenzie *et al.* 2007).

DHEA is the subject of extensive metabolism in various mammalian tissues. Although the main source of circulating DHEAS are the adrenals, both DHEA and DHEAS are formed also in the brain. Brain itself is a site of DHEA sulfurylation and hydrolysis, due to the high activity of steroid sulfotransferases and sulfatases. Another important steroid-metabolising reaction occurring in the brain is steroid 7-hydroxylation, resulting in 7α- and 7β-hydroxylated products, which have recently been reported to possess immunomodulatory and neuroprotective properties (reviewed in: Morfin *et al.* 2000; Morfin & Stárka 2001). Enzymes of the P450 family were found to be responsible for 7-hydroxylation in the brain in both rats and humans (Rose *et al.* 1997; Chalbot & Morfin 2006). The beneficial effects of 7-hydroxylated DHEA metabolites on immune function are of particular interest, because of the autoimmune theory of schizophrenia, as evidenced by the strong correlation between immunological effects and the pathophysiology of schizophrenia (Strous & Shoenfeld 2006). In fact, it has been suggested that 7-hydroxylated DHEA metabolites are locally active anti-glucocorticoids, responsible for counteracting the excessive effects of cortisol (Morfin & Stárka 2001; Hampl *et al.* 2002).

In addition to steroids and other hormones, such as prolactin, thyroid or sex hormones, various other laboratory parameters were investigated in the search for more accurate diagnostics for schizophrenia. In general, changes in the metabolome, the complex of biochemicals in body fluids and tissues, can indicate if abnormal biological processes are occurring. Thus, these changes have become the target of intense research efforts attempting to elucidate their role (Quinones & Kaddurah-Daouk 2009). In particular, the goal of such research is to identify biomarkers that would enable: prediction of the onset of illness, earlier diagnosis, and efficient treatment monitoring (Rachakonda *et al.* 2004). In addition to neurotransmission indicators and their respective signaling pathway components, the major biochemical markers which may be altered in schizophrenia include serum lipids (Casey 2004; Jakovljević *et al.* 2007), glycoregulation indicators (in particular metabolic syndrome indicators) (Haupt & Newcomer 2001; De Hert *et al.* 2009), and thyroid function parameters (Othman *et al.* 1994; Palha & Goodman 2006).

Specific metabolic parameters and their impairment (hyperglycaemia, risk of diabetes mellitus, dyslipidemia, metabolic syndrome, etc) both in schizophrenia, and as a negative consequence of antipsychotic drug therapy, have been the focus of great attention in both research and clinical practice in recent years (Meyer & Stahl, 2009; Newcomer, 2007). Similarly, DHEA/S and steroid levels have been intensively investigated. However, the role of neuroimmunomodulatory steroids remains poorly understood. In particular, to date, the levels of 7-hydroxylated DHEA metabolites in schizophrenia patients have not yet been studied.

The study aims were 1) to determine the levels of specific steroids and biochemical parameters in drug-naive schizophrenia patients compared to age-matched healthy controls, and 2) to evaluate the effect of treatment with atypical antipsychotics on the measured parameters.

PATIENTS AND METHODS

Study subjects

The study protocol used here was approved by the Ethical Committee of the Institute of Endocrinology; all study subjects signed an informed consent form.

The study group consisted of 22 drug-naive first-episode schizophrenia patients, diagnosed with either ICD-10 dg. paranoid schizophrenia (F 20.0, n=15) or undifferentiated schizophrenia (F 20.3, n=7). The study group included 13 males and 9 females, with a mean age of 32.6 years. Patients were treated with either olanzapine or non-olanzapine drugs as follows: olanzapine treated males (n=6, 10–15 mg/day); non-olanzapine

treated males (n=7, consisting of risperidone treated males, n=5, 3–4 mg/day and amisulpride treated males, n=2, 300 mg/day); olanzapine treated females (n=4, 15 mg/day); non-olanzapine treated females (n=5, consisting of risperidone treated females, n=4, 4 mg/day, and amisulpride treated females, n=1, 300 mg/day). Open-label antipsychotic treatment was prescribed using a flexible dosing schedule, which was adjusted at the treating physician's discretion. All the patients did not smoke during the study. The control group consisted of 25, healthy, age-matched females (mean age 35.0 years) and 22, healthy, age-matched males (mean age 31.0 years) drawn from a population sample.

Methods

The severity of schizophrenic illness in patients was assessed using the Clinical Global Impression Severity Scale (CGI-S). After obtaining informed consent and following diagnosis, blood samples were taken from all subjects (both the study and control groups). Blood samples were collected at 8:00 a.m., following overnight fasting, and subsequently used for hormonal and biochemical assays. Follow-up examination was performed after 6 months of stable treatment with atypical antipsychotic drugs.

Fasting blood glucose levels were measured with a Glucose analyser (Beckman, Fullerton, CA) using the glucoso-oxidase method.

Steroids, cortisol, dehydroepiandrosterone (and its sulfate DHEA/S) levels were measured using radioimmunoassay kits obtained from Beckman Coulter (previously Immunotech, Marseille, France). 7β-Hyd roxydehydroepiandrosterone (7βOH-DHEA) and its 7α-hydroxyisomer (7αOH-DHEA) were determined using an in-house radioimmunoassay as previously described (Lapčík *et al.* 1998; Lapčík *et al.* 1999).

Prolactin levels were measured using the PRL IRMA kit obtained from Immunotech. Thyroid parameters, including: thyrotropin (TSH) and free thyroxine (FT_4) were measured by ECLIA (obtained from Roche Diagnostics GmBH, Mannheim, Germany) using a commercial Elecsys System 2010. Anti-thyroid peroxidase (TPO Ab) and anti-thyroglobulin autoantibodies (Tg Ab were measured using an enzyme-linked immunosorbent assay (ELISA) (Aesku Diagnostics, Wendelsheim, FRG).

Lipid parameters, including total serum cholesterol, high- and low density lipoproteins, and triacylglycerides, were measured using commercially available kits CHOL2 HiCo T 400, HDL-C III 200, LDL-D Gen 2 200, and TRIGL 250, respectively (Roche Diagnostics GmbH) with a Cobas 6000 module C analyser.

In all tests where commercial kits were used, reference values and analytical parameters agreed with those reported by the manufacturer.

Selected thiol levels were measured as follows: the plasma concentration of homocysteine (Hcy) and other thiols (cysteine, cysteinylglycine and glutathione) were measured by high performance liquid chromatography (HPLC) equipped with fluorescence detection (Vester & Rasmussen 1991).

Statistical Analysis

Treatment effects were evaluated using a repeated measures ANCOVA. In addition to the previously mentioned main effects and subject factors as separating inter-individual variability and taking into account drug × therapy interaction, the ANCOVA model included interactions between the main effects. Due to the skewed data distribution and non-constant variance, the original data were transformed to symmetry and homoscedasticity using a power transformation. Differences between untreated subjects and controls were evaluated using a Mann-Whitney test.

RESULTS

Table 1 shows the serum levels of 19 biochemical parameters from 13 male drug-naive (first episode) patients diagnosed with schizophrenia, and 22, age-matched, healthy male controls. The data include five steroids (cortisol, DHEA, DHEA/S, and both 7-hydroxy-DHEA epimers), selected thyroid function parameters (including autoantibodies against thyroid peroxidase and thyroglobulin), prolactin levels, glucose levels, lipid spectrum measurements (triacylglycerides, total, HDL and LDL cholesterol), and 4 aminothiol levels (homocysteine, cysteine, cysteinylglycine and glutathione). The effects of 6 months therapy on 13 male schizophrenia patients treated with either non-olanzapine antipsychotics (n=7) or olanzapine (n=6) on the above mentioned parameters is shown on Table 2. Analogous results for 9 female schizophrenia patients, before and after antipsychotic treatment, and from 25, age-matched, healthy female controls are shown in Table 3. The smaller number of female schizophrenia patients prevented us from distinguishing between patients treated with non-olanzapine antipsychotics and olanzapine. The severity of schizophrenic illness, as measured by the CGI scale, decreased on average from 5 to 3. The data provided do not distinguish between the type of schizophrenia (paranoid or undifferentiated).

Concerning steroid levels, male schizophrenia patients displayed significantly lower DHEAS and 7α-OH-DHEA (one of DHEA 7-hydroxyisomers) levels compared to controls, whereas cortisol levels did not differ. At least male patients displayed much higher levels of autoantibodies against TPO ($p<0.001$). In both sex groups impaired lipid parameters and increased homocysteinemia were found, whereas glutathione levels were lower than in control subjects.

In both sexes, treatment with atypical antipsychotics did not result in significant changes in steroid levels or the biochemical parameters, with the exception of an increase of prolactinemia after non-olanzapine medication.

DISCUSSION

Circulating DHEA/S and cortisol levels and their ratios, have been extensively studied in a large number of neurological and psychiatric diseases, including schizophrenia, often with controversial results. Clinical trials concerning DHEA/S and pregnenolone have been extensively reviewed; e.g. see MacKenzie *et al.* 2007; Ritsner (2010). Two types of studies were conducted, in large part by Israeli authors such as Strous, Ritsner, Weizman and others (see references throughout the text). The first, dealt with steroid level alterations in medicated vs. non-medicated schizophrenia patients in comparison with control subjects (healthy, sex and age matched), and the correlation of these alterations with clinical symptoms and disease severity. In general, DHEA and DHEAS levels in schizophrenic and healthy subjects differed across all of these studies, and were mostly independent of the medication used in treatment. However, even higher DHEA/S levels were reported for non-medicated, first-episode schizophrenia subjects (Strous *et al.* 2004). The second line of studies addressed the clinical and laboratory effects of DHEA administration on schizophrenic patients, in an attempt to test the generally shared opinion that DHEA administration has a positive effect on patient well-being (Strous *et al.* 2003; Strous *et al.* 2007).

Tab. 1. Levels of nighteen biochemical parameters in 13 drug-naive male patients with schizophrenia and in 22 age-matched controls

Parameter	Unit	Patients	Controls
		Median (upper; lower quartile)	Median (upper; lower quartile)
Age	years	31 (25; 35)	31 (25; 33)
DHEAS	μmol/l	4.87 (2.76; 6.69)	9.3 (6.8; 11.9)***
DHEA	nmol/l	16.4 (13.6; 27.8)	28.0 (18.8; 31.8)
7αOH-DHEA	nmol/l	0.48 (0.44; 0.84)	1.34 (0.93; 1.51)**
7βOH-DHEA	nmol/l	0.89 (0.72; 1.36)	1.25 (0.94; 1.60)
Cortisol	nmol/l	469 (423; 526)	499 (411; 595)
Thyrotropin	mIU/l	1.21 (0.80; 1.80)	1.84 (1.40; 2.36)*
Free thyroxine	pmol/l	17.4 (16.0; 17.6)	15.7 (14.8; 17.0)
Tg Ab	pmol/l	10.0 (8.6; 11.1)	23.7 (12.5; 39.9)*
TPO Ab	IU/ml	10.5 (6.34; 16.3)	3.96 (2.38; 6.92)***
Prolactin	mIU/l	238 (116; 316)	237 (193; 264)
Glucose	mmol/l	4.15 (4.03; 5.09)	4.90 (4.50; 5.10)
Triacylglycerides	mmol/l	1.76 (0.97; 2.13)	0.83 (0.58; 0.97)**
Cholesterol	mmol/l	4.60 (4.12; 5.48)	4.11 (3.53; 4.45)*
HDL-Cholesterol	mmol/l	1.20 (1.12; 1.35)	1.48 (1.27; 1.66)*
LDL-Cholesterol	mmol/l	2.72 (2.11; 3.71)	2.45 (2.27; 2.80)
Homocysteine	μmol/l	15.6 (13.7; 19.4)	11.9 (10.0; 12.6)**
Cysteine	μmol/l	319 (260; 372)	235 (214; 278)**
Cysteinylglycine	μmol/l	29.6 (22.4; 37.6)	31.7 (25.3; 37.4)
Glutathione	μmol/l	2.01 (1.30; 2.51)	5.97 (3.55; 9.5)***

Provided are medians (upper; lower quartile) and significance (patients vs. controls): *p<0.05; **p<0.01; ***p<0.001 (Mann-Whitney test).
Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; 7αOH-DHEA, 7α-hydroxydehydroepiandrosterone; 7βOH-DHEA; 7β-hydroxydehydroepiandrosterone; Tg Ab, autoantibodies to thyroglobulin; TPO Ab, autoantibodies to thyroid peroxidase

In our male schizophrenia patients, we found only reduced DHEAS levels compared to healthy control subjects, in agreement with Ritsner *et al.* (2006), but in contrast with an earlier report by Strous *et al.* (2004), whereas differences in unconjugated DHEA levels were insignificant.

As expected, and in agreement with other authors (Casey et.al. 2004; Jakovljević *et al.* 2007; De Hert *et al.* 2009), our schizophrenia patients displayed an impaired lipid spectrum and, in the female group, higher prolactinemia (Halbreich *et al.* 2003; Kinon *et al.* 2003) and homocysteinemia (Brown and Susser 2005; Levine *et al.* 2005; Muntjewerff *et al.* 2006). In contrast, glutathione levels in schizophrenic patients from both sexes were significantly lower than in controls, supporting a positive role for glutathione as an endogenous antioxidant (Dean *et al.* 2009).

The 6-month treatment period did not lead to significant changes in steroid parameters (with the exception of a slight decrease in 7β-OH-DHEA levels), in agreement with previous reports (Ritsner *et al.* 2006; Ritsner *et al.* 2007). With the exception of an expected increase in prolactinemia after non-olanzapine treatment, the therapy outlined in this study had no statistically significant effect on the other biochemical parameters evaluated. This finding may be advantageous with respect to the predictive value of biochemical determinations and diagnosis. Somewhat surprisingly, antipsychotic drugs, including olanzapine, did not significantly increase the metabolic measures typically associated with this type of treatment (e.g., glucose, cholesterol and triacylglyceride levels). Based on these results, we intend to study the metabolome in schizophrenic patients in greater detail, with a particular emphasis on steroid metabolites, in order to enable earlier diagnosis of this disease using only selected biomarkers, similarly as we did in the past in the case of Alzheimer´s disease (Bičíková *et al.* 2004). It should be mentioned that, in spite of its beneficial effects, DHEA may be involved in events resulting in the augmentation of reactive oxygen species (ROS) in the brain, via its interaction with NMDA receptors (Strous 2005; MacKenzie *et al.* 2007). From this perspective, it should be noted that locally produced 7-hydroxylated DHEA metabolites are not known to possess any adverse effects, and, in fact, have been reported to have beneficial immuno- and neuroprotective effects (Morfin & Stárka 2001).

Tab. 2. CGI-S and levels of relevant steroids, basic thyroid- and lipid parameters, fasting glucose, prolactin and selected thiols in schizophrenia men before and after treatment with non-olanzapine (n=7) or olanzapine (n=6) antipsychotic medication.

		non-olanzapine		olanzapine		Ancova: effects of Drug; therapy (Ther); interindividual variability (Subj); Drug × Therapy interactions; followed by LSD multicomparisons Only significant differences are shown: *$p<0.05$; **$p<0.01$; ***$p<0.001$
Parameter	**Units**	**before therapy**	**after therapy**	**before therapy**	**after therapy**	
CGI-S	–	5 (4; 5)	3 (3; 3)	5 (4.25; 5)	3 (2.25; 3)	Ther***
7αOH-DHEA	nmol/l	0.53 (0.46; 0.69)	0.47 (0.42; 0.62)	0.44 (0.22; 0.83)	0.36 (0.20; 0.75)	Drug*; Subj(Drug)***
7βOH-DHEA	nmol/l	0.89 (0.77; 0.93)	0.78 (0.75; 0.93)	0.77 (0.47; 2.25)	0.64 (0.34; 0.87)	Ther**; Subj(Drug)***
DHEA	nmol/l	16.4 (13.9; 27.3)	21.4 (14.4; 24.5)	17.0 (12.8; 25.5)	15.1 (7.10; 29.2)	Drug**; Subj(Drug)***
DHEAS	μmol/l	5.09 (4.76; 6.79)	5.32 (5.10; 7.20)	3.61 (2.18; 4.77)	2.41 (1.69; 5.32)	Drug***; Subj(Drug)***
Cortisol	nmol/l	441 (394; 569)	612 (318; 635)	481 (440; 517)	464 (389; 534)	
Thyrotropin	mU/l	0.80 (0.69; 0.97)	1.53 (1.06; 1.68)	1.60 (1.31; 1.96)	1.38 (1.32; 1.47)	Subj(Drug)**
Free thyroxine	pmol/l	17.4 (15.0; 17.6)	16.8 (15.4; 18.0)	17.4 (16.0; 19.0)	17.0 (15.6; 17.9)	Subj***
TPO Ab	IU/ml	11.1 (10.2; 14.0)	11.0 (9.0; 19.8)	6.2 (5.2; 7.3)	7.90 (6.3; 8.1)	Drug***; Subj***
Tg Ab	pmol/l	10.5 (10.2; 11.1)	12.5 (11.4; 12.9)	8.6 (7.9; 10.0)	10.5 (8.5; 11.7)	Drug***; Ther*; Subj***
Prolactin	mIU/l	292 (176; 357)	990 (970; 1357)	202 (135; 273)	148 (119; 212)	Ther*; Drug xTher*
Fasting glucose	mmol/l	4.03 (3.62; 4.13)	3.58 (3.50; 4.26)	5.03 (4.52; 7.10)	5.08 (4.02; 5.52)	Drug**; Subj(Drug)**
Triacylglycerides	mmol/l	0.97 (0.81; 1.91)	1.12 (1.00; 1.87)	1.95 (1.59; 2.26)	2.08 (1.71; 2.60)	Subj(Drug)**
Cholesterol	mmol/l	4.40 (4.01; 5.52)	5.11 (4.55; 5.20)	4.94 (4.24; 5.67)	5.73 (4.48; 6.29)	Subj(Drug)**
HDL-cholesterol	mmol/l	1.27 (1.18; 1.36)	1.30 (1.28; 1.39)	1.16 (1.05; 1.22)	1.15 (1.07; 1.22)	Subj(Drug)*
LDL-cholesterol	mmol/l	2.72 (2.19; 3.32)	2.86 (2.58; 3.27)	3.16 (2.23; 3.91)	3.64 (2.74; 4.22)	Subj(Drug)**
Homocysteine	nmol/l	15.2 (10.3; 17.9)	13.7 (11.6; 16.0)	16.8 (14.8; 23.4)	14.8 (13.2; 16.7)	
Cysteine	μmol/l	260 (244; 298)	266 (255; 303)	373 (324; 447)	325 (285; 356)	
Cysteinylglycine	μmol/l	31.1 (20.8; 37.8)	27.0 (24.7; 33.1)	29.3 (27.1; 34.4)	40.2 (27.1; 50.0)	
Glutathione	μmol/l	2.01 (1.18; 2.42)	1.95 (1.57; 2.27)	2.01 (1.94; 2.44)	2.26 (1.83; 2.59)	Subj(Drug)**

Provided are medians (upper; lower quartile) and significance. Abbreviations: CGI-S: Clinical Global Impression Severity Scale; LSD: least square differences; other abbreviations as in the Table 1.

Finally, the high anti-TPO titres found in this study, which were highly significant in male patients, support the hypothesis of autoimmune participation in the etiopathology of the schizophrenia (Strous *et al.* 2006), and is in agreement with findings of thyroid autoantibodies in schizophrenic patients by other authors (Othman *et al.* 1994; Padmos *et al.* 2004; Laske *et al.* 2008; Poyraz *et al.* 2008).

CONCLUSION

In this study, 22 patients suffering from schizophrenia were compared with age-matched control subjects of both sexes, focusing on differences in adrenal steroid levels. We did not confirm earlier findings of others concerning DHEAS levels, which, at least in male patients, were decreased. However, for the first time, we report differences in 7-hydroxylated DHEA metabolites, especially the 7α-epimer (now believed to be a locally active neuroprotective and immunoprotective agent in the brain), which was reduced in the schizophrenia patient groups. The differences found for the other biochemical markers (lipid parameters, glucose levels, prolactin, thyroid hormones and homocysteine) were in agreement with data reported by others. However, we did not confirm the previously reported negative effects of antipsychotics on the biochemical parameters measured here. Our finding of high levels of anti-TPO autoantibodies supports the hypothesis that autoimmunity plays a role in schizophrenia. The fact that the parameters studied here do not depend on the type of antipsychotic medication may be advantageous with respect to the search for specific biochemical markers as a basis for improved schizophrenia diagnostics.

ACKNOWLEDGEMENTS

This work was supported by Grant No NS-8935-4 from the Internal Grant Agency of the Czech Ministry of Health.

Tab. 3. Serum levels of nighteen biochemical parameters in 9 drug-naive (first episode) female patients with schizophrenia and in 25 age-matched controls, and the effect of six month therapy of patients with atypic antipsychotics.

Parameter	Unit	Patients		Controls
		Before treatment	After treatment	
Age	years	34 (28; 34)	–	35 (30; 41)
DHEAS	μmol/l	5.30 (4.79; 5.96)	4.86 (3.44; 5.62)	4.70 (3.08; 5.50)
DHEA	nmol/l	19.5 (16.1; 30.4)	18.0 (15.2; 26.5)	16.6 (11.2; 25.3)
7αOH-DHEA	nmol/l	0.64 (0.60; 0.72)	0.51 (0.44; 0.71)	0.89 (0.33; 1.56)
7βOH-DHEA	nmol/l	1.05 (0.77; 1.62)	0.84 (0.64; 1.06)	1.16 (0.95; 1.61)
Cortisol	nmol/l	474 (385; 638)	427 (419; 599)	274 (214; 315)***
Thyrotropin	mIU/l	1.13 (0.81; 1.60)	2.11 (1.18; 2.79)	1.78 (1.43; 2.40)
Free thyroxine	pmol/l	15.3 (14.0; 17.7)	15.6 (14.9; 16.8)	15.1 (13.6; 16.2)
Tg Ab	pmol/l	9.6 (8.6; 10.0)	10.3 (10.0; 11.0)	12.3 (6.03; 25.1)
TPO Ab	IU/ml	9.0 (6.30; 9.74)	7.9 (7.3; 10.0)	4.88 (3.22; 9.25)
Prolactin	mIU/l	266 (177; 360)	479 (286; 564)	140 (104; 235)*
Glucose	mmol/l	4.29 (3.68; 4.98)	3.92 (3.60; 4.49)	4.55 (4.22; 4.96)
Triacylglycerides	mmol/l	1.33 (0.99; 1.71)	1.52 (081; 0.60)	0.56 (0.50; 0.69)*
Cholesterol	mmol/l	4.87 (4.38; 6.25)	5.33 (5.20; 6.10)	4.46 (4.21; 4.78)
HDL-cholesterol	mmol/l	1.40 (1.16; 1.44)	1.51 (1.22; 1.59)	1.82 (1.53; 1.98)*
LDL-cholesterol	mmol/l	2.84 (2.59; 4.14)	3.16 (2.85; 3.90)	2.18 (2.07; 2.70)*
Homocysteine	μmol/l	15.4 (10.5; 16.7)	14.0 (9.02; 15.2)	9.50 (7.19; 11.0)**
Cysteine	μmol/l	311 (293; 389)	301 (296; 354)	239 (216; 280)**
Cysteinylglycine	μmol/l	25.1 (22.6; 43.9)	33.6 (29.2; 44.0)	24.9 (22.3; 41.5)
Glutathione	μmol/l	1.66 (1.32; 2,86)	1.66 (1.50; 2.62)	6.9 (5.3; 10.8)***

Provided are medians (upper; lower quartile) and significance (patients vs. controls) *p<0.05; **p<0.01; ***p<0.001 (Mann-Whitney test). The type of antipsychotics (non-olanzapine or olanzapine) is not distinguished. Abbreviations as in the Table 1

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