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Elevated brain-derived neurotrophic factor (BDNF) serum levels in an acute episode of schizophrenia in polish women: Correlation with clinical and metabolic parameters.

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A B S T R A C T

Brain-derived neurotrophic factor (BDNF) has been implicated in the pathogenesis of psychiatric disorders. Schizophrenia is associated with metabolic abnormalities and BDNF regulates energy homeostasis and glucose metabolism in peripheral tissues. The aim of this study was to examine serum levels of BDNF in schizophrenic women during 8 weeks of treatment and control group, and its correlation with clinical and metabolic parameters. The study was performed on a group of 96 women: 55 diagnosed with paranoid schizophrenia according to DSM-IV criteria, and 41 healthy controls. Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of schizophrenia. BDNF serum levels and metabolic parameters: fasting serum glucose, total cholesterol, triglyceride (TG), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C) were measured at baseline and week 8 of treatment. BDNF serum levels were significantly elevated in medicated patients with schizophrenia comparing to controls. After 8 weeks of antipsychotic treatment, BDNF levels did not significantly change. Increase in TG and TG/HDL-C ratio and a decrease in HDL-C was detected in medicated patients. Correlation between BDNF and lipid profile as well as symptoms severity was found. In our study we detected abnormalities in BDNF levels and lipid profile in medicated schizophrenic women in Polish population.

1. Introduction

Serious mental illnesses are major contributors of the global burden and represent a big problem for public health (Whiteford et al., 2013). Psychiatric disorders are very heterogeneous diseases with the genetic and environmental compound. Neurotrophic factors have been widely implicated in neuropsychiatric disorders, including schizophrenia and depression (Shoval and Weizman, 2005).

Brain-derived neurotrophic factor (BDNF) is a neurotrophin widely expressed in human brain. It plays a key role in the regulation of growth, differentiation and survival of neurons in brain development. BDNF controls the development of dopaminergic, serotonergic, GABA-ergic and glutamatergic neurons (Angelucci et al., 2005) and exerts a significant effect on the neurogenesis and neuroplasticity (Numakawa et al., 2010). BDNF is mostly found in the hippocampus and cerebral cortex (Wetmore et al., 1990), parts of the brain which control cognition, mood and emotion. Abnormalities of synaptic plasticity, induced by impaired expression of BDNF, may cause anatomical and functional disturbances (Duman and Monteggia, 2006; Lang et al., 2004; Sen et al., 2008). On this basis, BDNF has been implicated in the pathophysiology of neurological and psychiatric disorders.

BDNF gene is located on chromosome 11p13 (Maisonpierre et al., 1991) and contains multiple alternative exons and one exon coding the pro-BDNF protein. Promoters of BDNF gene are regulated in developmental, tissue-specific and activity-dependent manner (Aid et al., 2007). Previous studies show that transport and local synthesis of BDNF in dendrites could regulate BDNF function (Chen et al., 2008).

Animal studies showed that brain and serum BDNF levels are positively correlated (Karege et al., 2002). Based on the studies indicating that Val66Met polymorphism can influence BDNF secretion in neurons and BDNF protein is transported across the blood–brain barrier (Pan et al., 1998), it is reasonable to study BDNF protein levels in serum or plasma and seek for the association between the functional polymorphism and circulating BDNF concentration.

Because metabolic dysregulation influences the brain functions, the disturbances in peripheral glucose regulation might be associated with cognitive impairment and schizophrenia development and are highly associated with obesity, metabolic syndrome and type-2 diabetes (Malhotra et al., 2013). Data from a population-based cohort studies show an association of schizophrenia with metabolic syndrome and

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impaired glucose (Cordes et al., 2016). BDNF is a regulator of energy homeostasis, has important effects on central regulation of food intake and body weight. BDNF expression was detected in several brain regions related to the regulation of eating behavior and energy balance control, including the hippocampus, hypothalamus, cortex, amygdala, nucleus of the solitary tract and substantia nigra. BDNF protein is synthesized not only in the central nervous system but also in peripheral tissues, i.e. skeletal and smooth muscles, liver, pancreas, endothelial cells, adipose tissue, lungs, heart and blood cells (eosinophils, monocytes, megakaryocytes), for review see (Briana and Malamitsi-Puchner, 2018).

1.1. Aim of the study

This is an observational study of schizophrenic inpatient women during 8 weeks of treatment with antipsychotics, comparing to the control group. We have focused on BDNF levels, clinical and metabolic parameters and theirs possible correlations.

The primary aim of the study was to compare BDNF levels in women with schizophrenia at baseline and after 8 weeks of treatment with the control group.

The secondary aim was to analyze BDNF levels with clinical (age, age of onset, tobacco smoking, family history of schizophrenia or other psychiatric disorders and severity of schizophrenia) and metabolic parameters (BMI, waist-to-height ratio, fasting serum glucose, cholesterol, triglyceride (TG), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C) and TG/HDL-C ratio).

Effect of antipsychotic dosage on BDNF level, clinical and metabolic parameters was analyzed.

2. Methods

2.1. Participants

Initially 62 patients with schizophrenia (57 females, 5 males) were recruited, 2 female patients with schizophrenia withdraw their consent for participation in the study. During recruitment, male patients more often refused to take part in the study, resulting in the sex ratio disproportion. Therefore, in the present study, we have decided to include only women to improve the homogeneity of the studied subgroups. Finally, the study was performed on a group of 96 women: 55 diagnosed with paranoid schizophrenia (mean age 32,36 years, SD = 9.88) and 41 healthy controls (mean age 42.02 years, SD = 13.46). Consensus diagnosis of schizophrenia was made by two experienced psychiatrists for each patient using Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1996). All patients were evaluated for lifetime psychiatric symptomatology with the Operational Criteria for Psychotic Illness (OPCRIT) (McGuffin et al., 1991). Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess the severity of schizophrenia. There were 19 drug-free patients. All patients with schizophrenia received atypical antipsychotics; 24 of them were additionally treated with typical antipsychotics. Chlorpromazine equivalents dosage were estimated.

Participants were recruited during the acute phase of illness from inpatients treated at the Department of Psychiatry, Poznan University of Medical Sciences. Clinical and biological parameters were evaluated at baseline and after 8 weeks of treatment. The control group consisted of healthy volunteers. Exclusion criteria were: chronic or acute somatic or neurological diseases, increased CRP (C-reactive protein). All subjects were of Caucasian origin and they were native Polish population from Great Poland region. The study was performed in accordance with the ethical standards established in the Declaration of Helsinki and was approved by the medical ethics committee of the Poznan University of Medical Sciences. All participants gave written informed consent before being included in the study, and their anonymity was preserved.

Patients were divided into drug-free (DF) and medicated (MED) subgroups. Influence of medication status and chlorpromazine equivalents on BDNF levels, metabolic and clinical parameters was examined. Adjustment for confounding factors: age, age of onset, illness duration, BMI, smoking status, family history of schizophrenia and other psychiatric disorders was performed. Analysis of BDNF levels with clinical (age, age of onset, PANSS total scores; positive, negative and general subscores) and metabolic parameters (fasting serum glucose, total cholesterol, HDL-C, LDL-C, TG, BMI, TG/HDL-C and waist-to-height ratio). TG/HDL-C and waist-to-height ratio are predictors of cardiometabolic risk (Weiler Miralles et al., 2015).

2.2. BDNF ELISA determination

10 ml of venous blood was withdrawn into anticoagulant-free tubes between 7.30 and 9.30 h after overnight fasting. After 1 h incubation, serum was separated by centrifugation, aliquoted and stored at − 70 until analyses. Enzyme-linked immunosorbent assay analyses were performed using DuoSet (cat. No DY 248) ELISA Development Kit (R&D System, Minneapolis, MN, USA) according to manufacturer's instructions, with minor modifications. Plates were coated with the capture antibody (2 μg/ml in PBS) overnight at 4 °C, then washed (3 times) and blocked for 3 h in reagent diluent (1% Bovine Serum Albumin (BSA)/ Phosphate Buffered Saline (PBS)). Serum samples were diluted 1:120 in reagent diluent to fit detection range of the standard curve. Plates were incubated with 100 μL of samples or standards overnight at 4 °C with shaking. All samples and standards were run in duplicates. Detection steps were performed strictly in accordance with the manufacturer's instructions. To avoid differences between assays, 16 patient samples at baseline and week 8, along with 8 control samples, were analyzed on the same plate. All plates were run within one week, on the same kit lot#, by the same experienced operator. Standard curves ranged from 1000–15.6 pg/ml. Intra-assay and inter-assay variability was $<5\%$ coefficient of variation (CV) and $<10\%$ CV (accordingly).

2.3. Metabolic parameters

Fasting serum glucose and lipid profile: cholesterol, triglyceride, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C) were measured at baseline and week 8, using the standard methods in the hospital diagnostic laboratory. Body mass index (BMI) was calculated by dividing weight by the square of height. TG/HDL-C ratio and waist-to-height ratio were calculated at baseline and week 8.

2.4. Statistical analyses

The Lillefors and Shapiro–Wilk tests were used to test the normality of the data. The homogeneity of variance of each variable was calculated with Levene's test. BDNF levels showed non-normal distribution and the homogeneity of variance was violated. BDNF levels were log-transformed prior the statistical analysis.

One-way ANOVA was used to compare BDNF levels and metabolic parameters at baseline between schizophrenia and control group. *T*-test for dependent variables was applied to estimate changes in BDNF concentrations, metabolic parameters and PANSS scores between baseline and week 8 measurements. Adjustment for confounding factors: age, age of onset, illness duration, BMI, waist-to-height ratio, smoking status, family history of schizophrenia and other psychiatric disorders was conducted using multivariate regression. Analysis of metabolic parameters with age and smoking status was performed using linear regression. Two-way ANOVA with repeated measures was applied to monitor changes in BDNF levels and metabolic parameters in medicated vs. drug-free patients during 8-weeks of treatment. Correlation with clinical and biochemical parameters was performed using Pearson's correlation test.

The statistical significance level was set at $p < 0.05$. Statistical analyses were conducted in Statistica v13 software .

Table 1
Clinical description of the studied group, metabolic parameters and BDNF serum levels (mean ± SD).

	Schizophrenia		Control group
Clinical description of the studied group			
Number (n)	55		41
Age (years)	32.36 ± 9.88		42.02 ± 13.46
Age of onset (years)	22.85 ± 4.93		NA
Early age of onset (≥18 years)	9		NA
Drug free (DF)	19		NA
Medicated (MED)	36		NA
Family history of schizophrenia	8		NA
Family history of other psychiatric disorders	12		NA
Medication			
Typical antipsychotics	24		NA
Haloperidol	19		NA
Zuclopenthixol	5		NA
Atypical antipsychotics	55		NA
	baseline	week 8	
Chlorpromazine equivalents (mean ± SD)	518.42 ± 356.06	582.1 ± 448.35	NA
PANSS scores (mean ± SD)			
PANSS Total	89.58 ± 12.58	62.86 ± 13.05	NA
PANSS Positive score	21.02 ± 3.73	12.43 ± 2.83	NA
PANSS Negative score	26.34 ± 5.83	20.33 ± 5.67	NA
PANSS General score	42.2 ± 6.45	30.13 ± 5.67	NA
Metabolic parameters (mean ± SD)			
BMI (kg/m^2)	25.49 ± 5.9	26.02 ± 4.94	–
Waist-to-height ratio	0.51 ± 0.08	0.53 ± 0.07	–
Cholesterol (total) (mg/dl)	205.78 ± 42.65	220.91 ± 47.24	213.3 ± 50.43
HDL-C (mg/dl)	56.79 ± 15.08	61.21 ± 14.25	61.41 ± 15.06
LDL-C (mg/dl)	123.15 ± 39.97	134.64 ± 43.74	132.33 ± 42.91
TG (mg/dl)	110.32 ± 50.48	124.18 ± 63.0	98.36 ± 58.56
TG/HDL-C ratio	2.63 ± 1.44	02.09 ± 1.17	1.73 ± 1.1
Fasting serum glucose (mg/dl)	90.9 ± 12.52	89.48 ± 10.61	95.54 ± 33.14
BDNF (mean ± SD)			
BDNF (ng/ml) - SCH total	31.94 ± 11.43	31.32 ± 12.36	22.69 ± 6.52
BDNF (ng/ml) - SCH MED	33.53 ± 11.13	32.89 ± 12.88	
BDNF (ng/ml) - SCH DF	28.91 ± 11.67	28.27 ± 10.99	

SCH MED – medicated patients;SCH DF - drug-free patients.

3. Results

Clinical characteristic and mean values of metabolic parameters (BMI, waist-to-height ratio, total cholesterol, HDL-C, LDL-C, TG, TG/HDL-C ratio, fasting serum glucose) and BDNF concentrations of the studied group are presented in Table 1.

There was significant decrease in PANSS total score ($t = 20.77$, $p < 0.01$) and PANSS subscales scores: positive ($t = 13.59$, $p < 0.01$), negative ($t = 13.74$, $p < 0.01$) and general ($t = 16.36$, $p < 0.01$) after 8-weeks treatment of schizophrenic patients.

There were no significant differences between metabolic parameters: total cholesterol, HDL-C, LDL-C, TG, TG/HDL-C ratio and fasting serum glucose between schizophrenia (MED + DF), as well as the DF subgroup and the controls at baseline. However, we found a significant increase in TG ($F = 4.12$, $p = 0.05$) and TG/HDL-C ratio ($F = 7.78$, $p < 0.01$) and decrease in HDL-C ($F = 6.32$, $p = 0.01$) in MED schizophrenia subgroup, comparing to the control group. After 8 weeks of antipsychotic medication, no significant changes in glucose and lipid profile were observed in MED + DF group as well as MED and DF subgroups (Table 2).

Table 2
Comparison of metabolic parameters and BDNF levels between schizophrenia at baseline and week 8 with control group.

Baseline						
	MED + DF		SCH MED		SCH DF	
	F	*p* value	*F*	*p* value	*F*	*p* value
Cholesterol (total)	0.64	0.43	0.06	0.8	1.13	0.29
HDL-C	1.56	0.21	6.32	**0.01**	0.31	0.58
LDL-C	1.14	0.29	0.05	0.82	2.17	0.15
TG	0.75	0.39	4.12	**0.05**	0.98	0.33
TG/HDL-C ratio	1.98	0.16	7.78	**0.007**	1.01	0.32
Fasting serum glucose	0.91	0.34	0.69	0.41	0.28	0.60
BDNF	16.63	**0.0001**	23.87	**0.00001**	3.34	0.07
Week 8						
	MED + DF		SCH MED		SCH DF	
	F	*p* value	*F*	*p* value	*F*	*p* value
Cholesterol (total)	0.38	0.53	0.005	0.94	0.92	0.34
HDL-C	0.004	0.95	0.38	0.53	0.9	0.34
LDL-C	0.032	0.88	0.10	0.74	0.34	0.56
TG	3.07	0.08	3.36	0.07	0.78	0.38
TG/HDL-C ratio	1.98	0.16	3.06	0.08	0.12	0.73
Fasting serum glucose	1.38	0.24	0.88	0.32	0.45	0.5
BDNF	11.8	**0.001**	13.16	**0.0005**	3.06	0.06

Statistical test: one-way ANOVA; SCH MED – medicated patients; SCH DF- drug-free patients.

Comparing metabolic parameters between MED and DF subgroups at baseline significant differences were observed for HDL-C ($F = 7.05$, $p = 0.01$), TG ($F = 9.84$, $p < 0.01$), TG/HDL-C ratio ($F = 9.9$, $p < 0.01$) and BMI ($F = 4.22$, $p = 0.04$). After 8-weeks of treatment there were no differences in metabolic parameters between MED and DF patients.

Influence of age on total cholesterol (SCH $F = 6.39$, $p = 0.01$; CON $F = 13.95$, $p < 0.01$), LDL-C (SCH $F = 8.20$, $p = 0.01$; CON $F = 17.3$, $p < 0.01$), TG (SCH $F = 4.45$, $p = 0.04$; CON $F = 5.89$, $p = 0.02$) and TG/HDL-C ratio in control group ($F = 6.35$, $p = 0.02$) was detected (Table 3). Smoking status did not affect metabolic parameters in the studied group.

Confounding factors: age ($F = 0.17$, $p = 0.68$), age of onset ($F = 0.08$, $p = 0.77$), illness duration ($F = 0.36$, $p = 0.55$), smoking status ($F = 1.0$, $p = 0.35$), family history of schizophrenia ($F = 0.78$, $p = 0.41$) and other psychiatric disorders ($F = 1.16$, $p = 0.22$) did not affect BDNF levels. At baseline waist-to-height ratio showed significant association with BDNF level ($F = 4.38$, $p = 0.04$); BMI ($F = 0.46$, $p = 0.5$) and TG/HDL-C ratio ($F = 2.17$, $p = 0.15$) were not associated with BDNF concentrations.

Comparing BDNF levels between MED + DF patients and healthy controls (CON), significant differences have been found at baseline ($F = 16.63$, $p < 0.01$) and week 8 ($F = 11.8$, $p < 0.01$). BDNF concentration was increased in schizophrenia. Statistical significance was higher comparing MED subgroup with CON at baseline ($F = 23.87$, $p < 0.01$) and week 8 ($F = 13.16$, $p < 0.01$). A statistical trend towards higher BDNF levels in DF subgroup at baseline ($F = 3.34$, $p = 0.07$) and week 8 ($F = 3.06$, $p = 0.06$) comparing to CON was found (Table 2). We detected lack of significant differences in BDNF levels between MED

Table 3
Analysis of BDNF and metabolic parameters with confounding factor: age.

	Schizophrenia		Control group	
	F	*p* value	*F*	*p* value
Cholesterol (total)	6.39	**0.01**	13.95	**0.0006**
HDL-C	1.76	0.19	0.90	0.34
LDL-C	8.20	**0.006**	17.30	**0.0002**
TG	4.45	**0.04**	5.89	**0.02**
TG/HDL-C ratio	3.13	0.08	6.35	**0.02**
Fasting serum glucose	0.0008	0.97	2.89	0.09
BDNF	0.59	0.44	0.61	0.43

Statistical test: linear regression analysis.

Table 4
Comparison of metabolic parameters and BDNF levels in medicated vs. drug free schizophrenia patients during 8 weeks of antipsychotic treatment.

	F	*p* value
BMI	2.7	0.11
Waist-to-height ratio	0.004	0.95
Cholesterol (total)	5.73	**0.02**
HDL-C	0.69	0.41
LDL-C	10.64	**0.003**
TG	1.85	0.18
TG/HDL-C ratio	1.54	0.22
Fasting serum glucose	0.22	0.88
BDNF	0.10	0.75

Statistical test: two-way ANOVA with repeated measures.

and DF patients at baseline ($F = 2.68$, $p = 0.1$) and at week 8 ($F = 1.1$, $p = 0.3$).

BDNF level changes between baseline and week 8 were not statistically significant in MED + DF ($t = 0.56$, $p = 0.57$), MED ($t = 0.74$, $p = 0.46$) and DF ($t = 0.06$, $p = 0.95$) subgroups.

Two-way ANOVA with repeated measures with MED/DF subgroups and baseline/week 8 change in metabolic parameters and BDNF levels detected significant differences in cholesterol ($F = 5.73$, $p = 0.02$) and LDL-C ($F = 10.64$, $p < 0.01$) (Table 4).

Analysis of chlorpromazine equivalents dose with clinical and metabolic parameters as well as BDNF levels shows significant correlation with baseline LDL-C ($F = 4.1$, $p = 0.02$) and TG/HDL-C ratio ($F = 9.81$, $p < 0.01$). Lack of influence of chlorpromazine equivalents dose on PANSS scores, other metabolic parameters and BDNF level at baseline and week 8 was detected (Table 5)

Baseline BDNF levels did not show any correlations with clinical or metabolic parameters. Positive correlations of BDNF levels at week 8 and PANSS scores at baseline: PANSS total ($r = 0.51$, $p < 0.01$), PANSS positive ($r = 0.48$, $p < 0.01$), PANSS negative ($r = 0.36$, $p = 0.05$), PANSS general ($r = 0.39$, $p = 0.02$) and week 8: PANSS total ($r = 0.42$, $p = 0.02$), PANSS positive ($r = 0.39$, $p = 0.03$), PANSS negative ($r = 0.41$, $p = 0.02$) were detected. BDNF level at week 8 positively correlated with baseline levels of: cholesterol ($r = 0.34$, $p = 0.04$), LDL-C ($r = 0.34$, $p = 0.04$), TG ($r = 0.34$, $p = 0.04$). Results of the correlation analysis are presented in Table 6.

No other correlations of BDNF levels with clinical and metabolic parameters studied were found.

4. Discussion

In our study, we found significantly elevated BDNF serum levels in medicated schizophrenic women compared to matched healthy controls. Disturbances in lipid profile (decrease in HDL-C, increase in TG and increase in TG/HDL-C ratio) were detected in medicated patients comparing to controls. Baseline differences between MED and DF patients was observed for HDL-C, TG, TG/HDL-C ratio and BMI. Influence of chlorpromazine equivalents dose on LDL-C and TG/HDL-C ratio was detected. Significant changes in cholesterol and LDL-C during 8 weeks of treatment with antipsychotics in DF patients comparing to MED patients were detected. Impact of age on metabolic parameters both in schizophrenia and control group on lipid profile was reported. Correlations of BDNF with clinical and metabolic parameters were detected.

Table 5
Analysis of chlorpromazine equivalents dosage with clinical, metabolic and BDNF parameters.

	Baseline		Week 8	
	F	*p* value	*F*	*p* value
PANSS Total	0.97	0.53	1.10	0.48
PANSS Positive	0.93	0.52	1.24	0.32
PANSS Negative	1.03	0.45	1.61	0.19
PANSS General	0.52	0.91	0.90	0.57
BMI	1.03	0.31	1.96	0.16
Waist-to-height ratio	2.43	0.12	2.19	0.14
Cholesterol (total)	0.52	0.89	0.65	0.78
HDL-C	0.44	0.96	0.63	0.82
LDL-C	4.10	**0.02**	0.83	0.66
TG	2.46	0.15	1.09	0.50
TG/HDL-C ratio	9.81	**0.003**	0.08	0.77
Fasting serum glucose	0.49	0.95	1.02	0.48
BDNF	0.97	0.50	1.30	0.25

Statistical test: one-way ANOVA.

Majority of the meta-analyses and reviews report decreased or unchanged BDNF serum/plasma levels in first-episode or chronic schizophrenia compared to the control group (Cui et al., 2012; Fernandes et al., 2015; Green et al., 2011; Libman-Sokolowska et al., 2015; Sanada et al., 2016; Toll and Mane, 2015). Late publications also report decreased or unchanged BDNF serum/plasma levels in the patients with schizophrenia during exacerbation compared to the healthy controls. In a recent study, during the 30-month trial on a large group of 305 patients with schizophrenia or schizoaffective disorder, Pillai et al. (2017) analyzed over 2300 samples in relapse, hospitalization or exacerbation state and found no differences between adverse outcomes (Pillai et al., 2017).

However, there are several studies that describe elevated BDNF levels in schizophrenia. Brazilian investigations report increased BDNF levels and correlation with PANSS scores in chronically institutionalized patients with schizophrenia (Reis et al., 2008), as well as in schizophrenic patients, compared the controls and euthymic bipolar disorder patients (Gama et al., 2007). Higher serum BDNF level was detected in other Brazilian schizophrenia group in the study on cognition (Asevedo et al., 2013) and cortical thickness (Zugman et al., 2015). More recent study by Penades et al. (2017) in the Spanish population also detected higher baseline serum BDNF level in schizophrenic patients compared to the healthy controls. Cognitive remediation applied in that study resulted in significant improvement in cognition and the quality of life, but did not influence BDNF levels (Penades et al., 2017). Skilleter et al. (2015) found increased plasma BDNF level in schizophrenia patients compared to healthy controls, in which the female patients displayed significantly higher BDNF levels than male patients and both male and female controls (Skilleter et al., 2015). Elevated serum BDNF concentration was recently reported in ultra-high risk of psychosis group (UHR) comprised of over 100 patients, although no support for a role in predicting outcome in UHR individuals was found (Yee et al., 2018). In our recently published study lack of differences in serum BDNF levesls between first-episode depressed women and control group was found (Skibinska et al., 2018). Comparing our schizophrenic and depressed female groups, we reported a significant increase of BDNF levels in schizophrenia,with the power of 95.18% (unpublished data). Both groups, along with the controls, were assayed at the same time using one DuoSet ELISA kit, which indicates that our results are not false positives.

Several of the human post-mortem studies in schizophrenia detected an increased expression of BDNF in cortical areas and hippocampus, but contradictory results were also reported (Libman-Sokolowska et al., 2015). Studies concerning antipsychotic treatment and BDNF expression in animal models and human studies are inconsistent: some show an increase in BDNF expression after antipsychotic administration, some do not report any influence of antipsychotics on BDNF mRNA and protein levels (de Bartolomeis et al., 2017). Observed increase in BDNF level in medicated schizophrenic patients in our study may be related to the action of antipsychotic treatment or a compensatory mechanism of the schizophrenia, or combination of both.

Altered lipid profile in our medicated subgroup with schizophrenia is in line with the previous findings, which consistently show that antipsychotic-associated dyslipidemia is described as elevation of serum

Table 6
Correlation of BDNF levels with clinical and metabolic parameters in schizophrenic patients.

	BDNF baseline baseline r	p value	week 8 r	p value	BDNF week 8 baseline r	p value	week 8 r	p value
PANSS Total	−0.04	0.84	−0.08	0.66	0.51	**0.004**	0.42	**0.02**
PANSS Positive	0.35	0.05	0.05	0.79	0.48	**0.007**	0.39	**0.03**
PANSS Negative	0.42	0.42	0.73	0.72	0.36	**0.05**	0.41	**0.02**
PANSS General	0.5	0.5	0.41	0.41	0.39	**0.02**	0.35	0.06
BMI	0.09	0.57	0.14	0.45	0.13	0.47	0.03	0.86
Waist-to-height ratio	0.14	0.47	0.15	0.40	0.15	0.40	0.21	0.25
Cholesterol (total)	0.1	0.55	0.15	0.4	0.34	**0.04**	0.23	0.17
HDL-C	−0.002	0.99	0.12	0.5	−0.07	0.68	0.11	0.52
LDL-C	0.09	0.59	0.09	0.61	0.34	**0.04**	0.24	0.16
TG	0.19	0.4	0.15	0.38	0.34	**0.04**	−0.1	0.55
TG/HDL-C ratio	0.14	0.4	0.1	0.56	0.29	0.07	−0.15	0.37
Fasting serum glucose	0.04	0.8	−0.05	0.79	0.08	0.62	−0.05	0.77

Statistical test: Pearson's correlation.

TG levels with modest alterations in other lipid profiles (Sharma et al., 2014). Similar to our results, lower HDL level in acute-phase schizophrenia was reported previously (Huang and Chen, 2005). Positive correlation of TG with BDNF levels found in our group is in line with findings by Nurjono et al. (2014). Similar trend was also reported in type 2 diabetes mellitus (Boyuk et al., 2014) and healthy female adolescents (Pedersen et al., 2017). Increase in TG/HDL-C ratio after 12-monthly antipsychotic treatment and association with BDNF Val66Met polymorphism was reported by Bonaccorso et al. (2015). Genetic study of Val66Met polymorphism in BDNF gene detected weak association with the clozapine-induced metabolic syndrome and fasting serum glucose level in males with schizophrenia (Zhang et al., 2013). Li et al. (2016) reported increased BDNF level in male schizophrenic patients with metabolic syndrome (Lin et al., 2017). Our results confirm previous findings concerning correlations of BDNF and metabolic disturbances in schizophrenia. It is possible that BDNF contributes to the pathophysiology of cardiovascular risk, or elevated circulating BDNF may represent a compensatory response to an underlying disease processes (Golden et al., 2010).

Significant differences in lipid profile between MED and DF patients were found in our study, what indicates psychotropic drug influence on these parameters.

Correlation of circulating BDNF level with the severity of schizophrenia symptoms, as measured by Positive and Negative Syndrome Scale (PANSS), was conducted in numerous studies, with inconsistent results. Lack of such correlation was demonstrated in drug-naïve/free (Bakirhan et al., 2017; Rizos et al., 2009; Simsek et al., 2015) or medicated schizophrenia patients (Lee et al., 2016; Noto et al., 2011; Pirildar et al., 2004; Strzelecki et al., 2016; Sun et al., 2016; Wysokinski, 2016; Yamamori et al., 2013; Yoshimura et al., 2016; Zhang et al., 2018). Relationships between higher BDNF levels and greater severity of the symptoms are reported in most of the studies which present correlations with PANSS (Ajami et al., 2014; Binford et al., 2018; Chen et al., 2009; Chiou and Huang, 2017; Kudlek Mikulic et al., 2017; Lee et al., 2011; Li et al., 2016; Reis et al., 2008; Rizos et al., 2008; Song et al., 2014; Tan et al., 2005a,b; Xiu et al., 2009; Yang et al., 2011; Zhang et al., 2015, 2014, 2016, 2010). Negative correlation between BDNF level and PANSS scores was reported in schizophrenia patients after electroconvulsive therapy (Li et al., 2016). In our study, only post-treatment serum BDNF levels positively correlated with PANSS total and subscales scores both at baseline and week 8, which is in line with the previous findings. It may indicate that in patients with more severe symptoms at baseline BDNF levels remains higher during treatment as compensatory mechanism.

During the last twenty years, numerous studied reported alterations in BDNF expression in the brain and peripheral blood in schizophrenia and other psychiatric disorders. Due to the contradictory results, caution must be taken during the interpretation of the results. The main limitations of the peripheral blood biomarker research are: heterogeneity of the studied groups, the limited number of participants and lack of comparisons between different ethnicities. Biomarkers research in psychiatric disorders needs to be replicated in randomized, controlled trials with larger studied groups. While specific biomarkers for psychiatric disorders could lead to an early diagnosis and proper treatment of the disease, they still should be thoroughly validated (Sigitova et al., 2017).

4.1. Conclusions

Alterations in BDNF serum levels and metabolic parameters was found in the presented study, which may result from disease mechanism or antipsychotic treatment, or combination of both. Association of BDNF with clinical and metabolic parameters was detected.

4.2. Limitations

The main limitation of the study is a relatively small study group comprising only female participants. There is a lack of data concerning hormonal status, which has been shown to correlate with BDNF level. Lack of BMI and waist-to-height ratio in the control group does not allow to compare those parameters between patients and healthy controls. ELISA kit used in the study did not distinguish between mature and proBDNF, therefore total BDNF was measured in our research.

Conflict of interest

None.

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Supplementary materials

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References

Aid, T., Kazantseva, A., Piirsoo, M., Palm, K., Timmusk, T., 2007. Mouse and rat BDNF gene structure and expression revisited. J. Neurosci. Res. 85 (3), 525–535.

Ajami, A., Hosseini, S.H., Taghipour, M., Khalilian, A., 2014. Changes in serum levels of brain derived neurotrophic factor and nerve growth factor-beta in schizophrenic patients before and after treatment. Scand. J. Immunol. 80 (1), 36–42.

Angelucci, F., Brene, S., Mathe, A.A., 2005. BDNF in schizophrenia, depression and corresponding animal models. Mol. Psychiatry 10 (4), 345–352.

Asevedo, E., Gadelha, A., Noto, C., Mansur, R.B., Zugman, A., Belangero, S.I., et al., 2013. Impact of peripheral levels of chemokines, BDNF and oxidative markers on cognition in individuals with schizophrenia. J. Psychiatr. Res. 47 (10), 1376–1382.

Bakirhan, A., Yalcin Sahiner, S., Sahiner, I.V., Safak, Y., Goka, E., 2017. Association of serum brain derived neurotropic factor with duration of drug-naive period and positive-negative symptom scores in drug naive schizophrenia. PLoS One 12 (12), e0189373.

Binford, S.S., Hubbard, E.M., Flowers, E., Miller, B.L., Leutwyler, H., 2018. Serum BDNF is positively associated with negative symptoms in older adults with schizophrenia. Biol. Res. Nurs. 20 (1), 63–69.

Bonaccorso, S., Sodhi, M., Li, J., Bobo, W.V., Chen, Y., Tumuklu, M., et al., 2015. The brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with increased body mass index and insulin resistance measures in bipolar disorder and schizophrenia. Bipolar Disord 17 (5), 528–535.

Boyuk, B., Degirmencioglu, S., Atalay, H., Guzel, S., Acar, A., Celebi, A., et al., 2014. Relationship between levels of brain-derived neurotrophic factor and metabolic parameters in patients with type 2 diabetes mellitus. J. Diabetes Res., 978143.

Briana, D.D., Malamitsi-Puchner, A., 2018. Developmental origins of adult health and disease: the metabolic role of BDNF from early life to adulthood. Metabolism 81, 45–51.

Chen, D.C., Wang, J., Wang, B., Yang, S.C., Zhang, C.X., Zheng, Y.L., et al., 2009. Decreased levels of serum brain-derived neurotrophic factor in drug-naive first-episode schizophrenia: relationship to clinical phenotypes. Psychopharmacology (Berl) 207 (3), 375–380.

Chen, Z.Y., Bath, K., McEwen, B., Hempstead, B., Lee, F., 2008. Impact of genetic variant BDNF (Val66Met) on brain structure and function. Novartis Found Symp. 289, 180–188 discussion 188-195.

Chiou, Y.J., Huang, T.L., 2017. Serum brain-derived neurotrophic factors in Taiwanese patients with drug-naive first-episode schizophrenia: Effects of antipsychotics. World J. Biol. Psychiatry 18 (5), 382–391.

Cordes, J., Bechdolf, A., Engelke, C., Kahl, K.G., Balijepalli, C., Losch, C., et al., 2016. Prevalence of metabolic syndrome in female and male patients at risk of psychosis. Schizophr. Res. 181, 38–42.

Cui, H., Jin, Y., Wang, J., Weng, X., Li, C., 2012. Serum brain-derived neurotrophic factor (BDNF) levels in schizophrenia: a systematic review. Shanghai Arch. Psychiatry 24 (5), 250–261.

de Bartolomeis, A., Buonaguro, E.F., Latte, G., Rossi, R., Marmo, F., Iasevoli, F., et al., 2017. Immediate-early genes modulation by antipsychotics: translational implications for a putative gateway to drug-induced long-term brain changes. Front Behav. Neurosci. 11, 240.

Duman, R.S., Monteggia, L.M., 2006. A neurotrophic model for stress-related mood disorders. Biol. Psychiatry 59 (12), 1116–1127.

Fernandes, B.S., Steiner, J., Berk, M., Molendijk, M.L., Gonzalez-Pinto, A., Turck, C.W., et al., 2015. Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: meta-analysis and implications. Mol. Psychiatry 20 (9), 1108–1119.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J., 1996. Structured clinical interview for DSM-IV Axis I disorders, clinician version (SCID-CV). American Psychiatric Press, Inc., Washington, D.C.

Gama, C.S., Andreazza, A.C., Kunz, M., Berk, M., Belmonte-de-Abreu, P.S., Kapczinski, F., 2007. Serum levels of brain-derived neurotrophic factor in patients with schizophrenia and bipolar disorder. Neurosci. Lett. 420 (1), 45–48.

Golden, E., Emiliano, A., Maudsley, S., Windham, B.G., Carlson, O.D., Egan, J.M., et al., 2010. Circulating brain-derived neurotrophic factor and indices of metabolic and cardiovascular health: data from the Baltimore Longitudinal Study of Aging. PLoS One 5 (4), e10099.

Green, M.J., Matheson, S.L., Shepherd, A., Weickert, C.S., Carr, V.J., 2011. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. Mol. Psychiatry 16 (9), 960–972.

Huang, T.L., Chen, J.F., 2005. Serum lipid profiles and schizophrenia: effects of conventional or atypical antipsychotic drugs in Taiwan. Schizophr. Res. 80 (1), 55–59.

Karege, F., Schwald, M., Cisse, M., 2002. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. Neurosci. Lett. 328 (3), 261–264.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Kudlek Mikulic, S., Mihaljevic-Peles, A., Sagud, M., Bajs Janovic, M., Ganoci, L., Grubisin, J., et al., 2017. Brain-derived neurotrophic factor serum and plasma levels in the treatment of acute schizophrenia with olanzapine or risperidone: 6-week prospective study. Nord. J. Psychiatry 71 (7), 513–520.

Lang, U.E., Hellweg, R., Gallinat, J., 2004. BDNF serum concentrations in healthy volunteers are associated with depression-related personality traits. Neuropsychopharmacology 29 (4), 795–798.

Lee, A.H., Lange, C., Ricken, R., Hellweg, R., Lang, U.E., 2011. Reduced brain-derived neurotrophic factor serum concentrations in acute schizophrenic patients increase during antipsychotic treatment. J. Clin. Psychopharmacol. 31 (3), 334–336.

Lee, J., Nurjono, M., Lee, T.S., 2016. Levels of serum brain-derived neurotrophic factor in schizophrenia. J. Nerv. Ment. Dis. 204 (8), 636–639.

Li, J., Ye, F., Xiao, W., Tang, X., Sha, W., Zhang, X., Wang, J., 2016. Increased serum brain-derived neurotrophic factor levels following electroconvulsive therapy or antipsychotic treatment in patients with schizophrenia. Eur. Psychiatry 36, 23–28.

Libman-Sokolowska, M., Drozdowicz, E., Nasierowski, T., 2015. BDNF as a biomarker in the course and treatment of schizophrenia. Psychiatr. Pol. 49 (6), 1149–1158.

Lin, C.C., Hung, Y.Y., Tsai, M.C., Huang, T.L., 2017. Increased serum brain-derived neurotrophic factor in male schizophrenic patients with metabolic syndrome. Medicine (Baltimore) 96 (22), e7089.

Maisonpierre, P.C., Le Beau, M.M., Espinosa, R., Ip, N.Y., Belluscio, L., de la Monte, S.M., Squinto, S., et al., 1991. Human and rat brain-derived neurotrophic factor and neurotrophin-3: gene structures, distributions, and chromosomal localizations. Genomics 10 (3), 558–568.

Malhotra, N., Grover, S., Chakrabarti, S., Kulhara, P., 2013. Metabolic syndrome in schizophrenia. Indian J. Psychol. Med. 35 (3), 227–240.

McGuffin, P., Farmer, A., Harvey, I., 1991. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. Arch. Gen. Psychiatry 48 (8), 764–770.

Noto, C.S., Gadelha, A., Belangero, S.I., Smith, M.A., de Aguiar, B.W., Panizzuti, B., et al., 2011. Association of biomarkers and depressive symptoms in schizophrenia. Neurosci. Lett. 505 (3), 282–285.

Numakawa, T., Suzuki, S., Kumamaru, E., Adachi, N., Richards, M., Kunugi, H., 2010. BDNF function and intracellular signaling in neurons. Histol. Histopathol. 25 (2), 237–258.

Nurjono, M., Tay, Y.H., Lee, J., 2014. The relationship between serum brain-derived neurotrophic factor (BDNF) and cardiometabolic indices in schizophrenia. Schizophr. Res. 157 (1-3), 244–248.

Pan, W., Banks, W.A., Fasold, M.B., Bluth, J., Kastin, A.J., 1998. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 37 (12), 1553–1561.

Pedersen, N.H., Tarp, J., Andersen, L.B., Gejl, A.K., Huang, T., Peijs, L., et al., 2017. The association between serum brain-derived neurotrophic factor and a cluster of cardiovascular risk factors in adolescents: the CHAMPS-study DK. PLoS One 12 (10), e0186384.

Penades, R., Lopez-Vilchez, I., Catalan, R., Arias, B., Gonzalez-Rodriguez, A., Garcia-Rizo, C., et al., 2017. BDNF as a marker of response to cognitive remediation in patients with schizophrenia: a randomized and controlled trial. Schizophr. Res. https://doi.org/10.1016/j.schres.2017.12.002.

Pillai, A., Schooler, N.R., Peter, D., Looney, S.W., Goff, D.C., Kopelowicz, A., et al., 2017. Predicting relapse in schizophrenia: is BDNF a plausible biological marker? Schizophr. Res. https://doi.org/10.1016/j.schres.2017.06.059.

Pirildar, S., Gonul, A.S., Taneli, F., Akdeniz, F., 2004. Low serum levels of brain-derived neurotrophic factor in patients with schizophrenia do not elevate after antipsychotic treatment. Prog. Neuropsychopharmacol. Biol. Psychiatry 28 (4), 709–713.

Reis, H.J., Nicolato, R., Barbosa, I.G., Teixeira do Prado, P.H., Romano-Silva, M.A., Teixeira, A.L., 2008. Increased serum levels of brain-derived neurotrophic factor in chronic institutionalized patients with schizophrenia. Neurosci. Lett. 439 (2), 157–159.

Rizos, E.N., Rontos, I., Laskos, E., Arsenis, G., Michalopoulou, P.G., Vasilopoulos, D., et al., 2008. Investigation of serum BDNF levels in drug-naive patients with schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 32 (5), 1308–1311.

Rizos, E.N., Siafakas, N., Stefanis, N., Douzenis, A., Kontaxakis, V., Laskos, E., et al., 2009. Association of serum BDNF and val66met polymorphism of the brain-derived neurotrophic factor in a sample of first psychotic episode patients. Psychiatriki 20 (4), 297–304.

Sanada, K., Zorrilla, I., Iwata, Y., Bermudez-Ampudia, C., Graff-Guerrero, A., Martinez-Cengotitabengoa, M., et al., 2016. The efficacy of non-pharmacological interventions on brain-derived neurotrophic factor in schizophrenia: a systematic review and meta-analysis. Int. J. Mol. Sci. 17 (10) pii: E1766.

Sen, S., Duman, R., Sanacora, G., 2008. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol. Psychiatry 64 (6), 527–532.

Sharma, E., Rao, N.P., Venkatasubramanian, G., 2014. Association between antipsychotic-induced metabolic side-effects and clinical improvement: a review on the evidence for "metabolic threshold". Asian J. Psychiatr. 8, 12–21.

Shoval, G., Weizman, A., 2005. The possible role of neurotrophins in the pathogenesis and therapy of schizophrenia. Eur. Neuropsychopharmacol. 15 (3), 319–329.

Sigitova, E., Fisar, Z., Hroudova, J., Cikankova, T., Raboch, J., 2017. Biological hypotheses and biomarkers of bipolar disorder. Psychiatry Clin. Neurosci. 71 (2), 77–103.

Simsek, S., Gencoglan, S., Yuksel, T., Kaplan, I., Aktas, H., 2015. Lower brain-derived neurotropic factor levels in untreated adolescents with first-episode psychosis. J. Clin. Psychopharmacol. 35 (5), 596–599.

Skibinska, M., Kapelski, P., Rajewska-Rager, A., Pawlak, J., Szczepankiewicz, A., Narozna, B., et al., 2018. Brain-derived neurotrophic factor (BDNF) serum level in women with first-episode depression, correlation with clinical and metabolic parameters. Nord. J. Psychiatry 72 (3), 191–196.

Skilleter, A.J., Weickert, C.S., Vercammen, A., Lenroot, R., Weickert, T.W., 2015. Peripheral BDNF: a candidate biomarker of healthy neural activity during learning is disrupted in schizophrenia. Psychol. Med. 45 (4), 841–854.

Song, X., Fan, X., Li, X., Kennedy, D., Pang, L., Quan, M., Chen, X., et al., 2014. Serum levels of BDNF, folate and homocysteine: in relation to hippocampal volume and psychopathology in drug naive, first episode schizophrenia. Schizophr. Res. 159 (1), 51–55.

Strzelecki, D., Kaluzynska, O., Wysokinski, A., 2016. BDNF serum levels in schizophrenic patients during treatment augmentation with sarcosine (results of the PULSAR study). Psychiatry Res. 242, 54–60.

Sun, Z.L., Liu, J., Guo, W., Jiang, T., Ma, C., Li, W.B., et al., 2016. Serum brain-derived neurotrophic factor levels associate with cognitive improvement in patients with schizophrenia treated with electroacupuncture. Psychiatry Res. 244, 370–375.

Tan, Y.L., Zhou, D.F., Cao, L.Y., Zou, Y.Z., Zhang, X.Y., 2005a. Decreased BDNF in serum of patients with chronic schizophrenia on long-term treatment with antipsychotics. Neurosci. Lett. 382 (1-2), 27–32.

Tan, Y.L., Zhou, D.F., Zhang, X.Y., 2005b. Decreased plasma brain-derived neurotrophic factor levels in schizophrenic patients with tardive dyskinesia: association with dyskinetic movements. Schizophr. Res. 74 (2-3), 263–270.

Toll, A., Mane, A., 2015. Brain-derived neurotrophic factor levels in first episode of psychosis: a systematic review. World J. Psychiatry 5 (1), 154–159.

Weiler Miralles, C.S., Wollinger, L.M., Marin, D., Genro, J.P., Contini, V., Morelo Dal Bosco, S., 2015. Waist-to-height ratio (WHtR) and triglyceride to HDL-C ratio (TG/HDL-c) as predictors of cardiometabolic risk. Nutr. Hosp. 31 (5), 2115–2121.

Wetmore, C., Ernfors, P., Persson, H., Olson, L., 1990. Localization of brain-derived neurotrophic factor mRNA to neurons in the brain by in situ hybridization. Exp. Neurol. 109 (2), 141–152.

Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., et al., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382 (9904), 1575–1586.

Wysokinski, A., 2016. Serum levels of brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) in depressed patients with schizophrenia. Nord. J. Psychiatry 70 (4), 267–271.

Xiu, M.H., Hui, L., Dang, Y.F., Hou, T.D., Zhang, C.X., Zheng, Y.L., et al., 2009. Decreased serum BDNF levels in chronic institutionalized schizophrenia on long-term treatment with typical and atypical antipsychotics. Prog. Neuropsychopharmacol. Biol. Psychiatry 33 (8), 1508–1512.

Yamamori, H., Hashimoto, R., Ishima, T., Kishi, F., Yasuda, Y., Ohi, K., et al., 2013. Plasma levels of mature brain-derived neurotrophic factor (BDNF) and matrix metalloproteinase-9 (MMP-9) in treatment-resistant schizophrenia treated with clozapine. Neurosci. Lett. 556, 37–41.

Yang, Y.Q., Sun, S., Yu, Y.Q., Li, W.J., Zhang, X., Xiu, M.H., et al., 2011. Decreased serum brain-derived neurotrophic factor levels in schizophrenic patients with tardive dyskinesia. Neurosci. Lett. 502 (1), 37–40.

Yee, J.Y., Lee, T.S., Lee, J., 2018. Levels of serum brain-derived neurotropic factor in individuals at ultra-high risk for psychosis - findings from the Longitudinal Youth at Risk Study (LYRIKS). Int. J. Neuropsychopharmacol. https://doi.org/10.1093/ijnp/pyy036.

Yoshimura, R., Hori, H., Katsuki, A., Atake, K., Nakamura, J., 2016. Serum levels of brain-derived neurotrophic factor (BDNF), proBDNF and plasma 3-methoxy-4-hydroxyphenylglycol levels in chronic schizophrenia. Ann. Gen. Psychiatry 15 (1). https://doi.org/10.1186/s12991-015-0084-9.

Zhang, X.Y., Chen, D.C., Tan, Y.L., Tan, S.P., Wang, Z.R., Yang, F.D., et al., 2015. The interplay between BDNF and oxidative stress in chronic schizophrenia. Psychoneuroendocrinology 51, 201–208.

Zhang, X.Y., Chen, D.C., Tan, Y.L., Tan, S.P., Wang, Z.R., Yang, F.D., et al., 2014. Gender difference in association of cognition with BDNF in chronic schizophrenia. Psychoneuroendocrinology 48, 136–146.

Zhang, X.Y., Tan, Y.L., Chen, D.C., Tan, S.P., Yang, F.D., Wu, H.E., et al., 2016. Interaction of BDNF with cytokines in chronic schizophrenia. Brain Behav. Immun. 51, 169–175.

Zhang, X.Y., Xiu, M.H., Chen, D.C., Yang, F.D., Wu, G.Y., Lu, L., et al., 2010. Nicotine dependence and serum BDNF levels in male patients with schizophrenia. Psychopharmacology (Berl) 212 (3), 301–307.

Zhang, Y., Chen, M., Wu, Z., Chen, J., Yu, S., Fang, Y., et al., 2013. Association study of Val66Met polymorphism in brain-derived neurotrophic factor gene with clozapine-induced metabolic syndrome: preliminary results. PLoS One 8 (8), e72652.

Zhang, Y., Fang, X., Fan, W., Tang, W., Cai, J., Song, L., et al., 2018. Brain-derived neurotrophic factor as a biomarker for cognitive recovery in acute schizophrenia: 12-week results from a prospective longitudinal study. Psychopharmacology (Berl) 235 (4), 1191–1198.

Zugman, A., Pedrini, M., Gadelha, A., Kempton, M.J., Noto, C.S., Mansur, R.B., et al., 2015. Serum brain-derived neurotrophic factor and cortical thickness are differently related in patients with schizophrenia and controls. Psychiatry Res. 234 (1), 84–89.