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High serum levels of FGF21 are decreased in bipolar mania patients during psychotropic medication treatment and are associated with increased metabolism disturbance

Qing Hu[a,1], Cong Wang[b,1], Farong Liu[a], Jue He[a], Fen Wang[c,**], Wenqiang Wang[a,*], Pan You[a,*]

[a] Xiamen City Xianyue Hospital, Xiamen, Fujian, China
[b] School of Pharmacy, Wenzhou Medical University, Wenzhou, Zhejiang, China
[c] Center for Translational Cancer Research, Institute of Biosciences and Technology, Texas A&M Health Science Center, Houston, TX, United States

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ABSTRACT

Bipolar disorder (BD), a psychiatric illness, results partly as a side effect of psychotropic medications and presents a high risk of metabolic disturbance. Fibroblast growth factor 21 (FGF21) is as an important regulator in carbohydrate and lipid metabolism. In this study, we investigated the serum levels of FGF21 and analyzed its association with metabolic parameters in bipolar mania patients at pre- and post-treatment with psychotropic medications. Bipolar mania inpatients (n = 99) and healthy controls (n = 99) were included at baseline; the patients were followed up after four-week treatment. Serum levels of FGF21 and several metabolic parameters were measured by appropriate detection methods. We found that baseline serum FGF21 levels were significantly higher in bipolar manic patients when compared to that in controls. After four-week medication, FGF21 levels were found to be decreased in patients when compared to the baseline suggesting that FGF21 may be associated with the psychopathology of bipolar mania. Moreover, FGF21 levels were found to be negatively correlated with the serum triglycerides (TG), cholesterol (CHO), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), glucose (Glu), and Body Mass Index (BMI). In addition, our data also indicates that FGF21 may monitor and/or prevent the metabolic abnormalities induced by psychotropic drugs.

1. Introduction

Bipolar disorder (BD) is a chronic psychiatric illness characterized by severe symptoms and recurrent episodes. BD is closely linked to psychiatric and medical complications (Merikangas et al., 2011). A recent study reported that bipolar disorder is the eighteenth most disabling health condition worldwide (Grande et al., 2016). The illness manifests itself as a lifetime of recurring mood disorders accompanied by elevated mood (mania or hypomania) or depression. Mania leads to a marked impairment in normal day-to day functions and appearance of hallucinations and/or delusions which may result in the hospitalization (Bobo, 2017).

The preferred choice of treatment for manic episode of bipolar disorder is drug therapy (Geddes and Miklowitz, 2013). However, patients with bipolar disorder have a very high mortality rate with cardiovascular (CV) disease as the leading cause of death.Moreover, the psychotropic medications used for treating BD are associated with potential risks of poor clinical metabolism (Calkin et al., 2013). a. Antipsychotic drugs such as risperidone, olanzapine and aripiprazole have been reported to cause weight gain or hyperlipidemia (Filakovic et al., 2012; Nihalani et al., 2012). It is worth noting that metabolic side effects occur early with the use of certain psychotropic drugs through a modulatory effect on the neural hormone system (Olfson et al., 2006). Patients with bipolar disorder and metabolic disorder have more serious disease symptoms and have a stronger resistance to treatment which further leads to increased medical and psychiatric burden of bipolar disorder (Calkin et al., 2013). Thus, special attention should be paid in assessing the risk of metabolic dysfunction in bipolar subjects in addition to appropriate prevention, screening, early detection and treatment.

Fibroblast growth factors (FGFs) family is comprised of 22 structurally related proteins that play a critical role in development, metabolism, and neuronal functions (Ornitz and Itoh, 2015). Studies on FGFs in human diseases suggest their physiological and pathophysiological

* Corresponding authors: Xiamen City Xianyue Hospital, Xiamen, Fujian 361012, China.
** Corresponding author: Institute of Biosciences And Technology, Texas A&M Health Science Center, Houston, Texas 77030, United States.
E-mail addresses: fwang@ibt.tmc.edu (F. Wang), wwq5392616@sina.com (W. Wang), panyou001@yahoo.com (P. You).
[1] Equal contribution.

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roles as well as diagnostic and therapeutic potential in metabolic diseases (Itoh et al., 2015). Recent evidence suggests that FGF expression changes in response to psychiatric medication for mental and psychological disease (Hashimoto et al., 2003; He et al., 2014). Fibroblast growth factor 21, a member of FGF superfamily, has been recognized as an important regulator of carbohydrate and lipid metabolism and body weight homeostasis (Itoh, 2014). It is mainly secreted by the liver (Nishimura et al., 2000) although it has also been identified in other tissues, such as pancreas, adipose, heart, and brain neurons (Leng et al., 2015). FGF21 has been reported to play a multifaceted role in physiopathology and metabolism (Giralt et al., 2015). When administered systemically in diabetic monkeys and in obese and insulin resistant rodents, FGF21 improved lipid metabolism and insulin sensitivity and led to a weight loss. In mice, FGF21 levels were elevated in response to starvation and the ketogenic state and were decreased by feeding (Dostalova et al., 2008). However, in clinical studies, the serum level of FGF21 was found to be significantly higher in patients with obesity, diabetes, fatty liver disease, and other related complications (Goldstein et al., 2013; Nihalani et al., 2012). Since neuropsychiatric disorders are more likely to cause metabolic disturbance, few reports have explored the role of FGF21 in mental disorders. Studies found that serum FGF21 levels in patients with schizophrenia (SZ) were significantly higher than that in healthy controls and were markedly correlated with the levels of serum metabolites involved in tricarboxylic acid (TCA) cycle (Qing et al., 2015). A recent study showed that FGF21 level increased significantly after Valproate (VPA) treatment and correlated with the treatment response and metabolic effects in depressed bipolar II disorder patients (Chang et al., 2018). These observations provide further support to the notion that FGF21 may play a role in etiology and treatment of mental diseases.

To the best of our knowledge, FGF21 has not been studied in manic patients with BD. Considering the pharmacological therapy and aberrant metabolism in bipolar disorder and the important metabolic role of FGF21, we hypothesized that FGF21 may be associated with metabolic changes and/or the treatment efficacy in patients with bipolar mania. We investigated serum levels of FGF21 and analyzed its association with clinical characteristics, especially metabolic parameters, in bipolar mania patients before and after treatment with psychotropic medications.

2. Materials and methods

2.1. Study subjects

A total of 99 inpatients diagnosed with bipolar mania with or without psychotic symptoms, according to the ICD-10 Tenth Edition criteria were included in the study. The recruited patients were either treatment naive or treatment free for at least 4 weeks before inclusion. Patients with bipolar disorder presenting during euthymic / depressive /mixed episode or patients with other neurotic disorders, pregnant and nursing women were excluded. For healthy controls, 99 age and sex matched people with no personal or first-degree family history of a psychiatric disorder were selected. All subjects were recruited at Xiamen Xianyue Hospital, Fujian, China. Institutional review board approval was obtained from the ethics committee of the hospital.

2.2. Psychotropic medication treatment of mania

Ninety-nine bipolar manic inpatients received specialized treatment with a second-generation antipsychotic drug (SGA) in conjunction with a mood stabilizer (MS) following diagnosis. Eighty-two patients did not receive any other types of treatment except for psychotropic medication during the course of the study. Detailed information on clinical psychotropic drugs used in these patients is included in supplemental Table S1. In addition to the psychotropic medication, 17 patients received lipid lowering agents or hypotensive drugs as appropriate. Thus, they were excluded from the follow-up studies (data not shown). Trained nurses documented patients' behavior with the 30-item Nurses' Observation Scale for Inpatient Evaluation (NOSIE-30) for inpatient evaluation at baseline and 4 weeks after the treatment.

2.3. Laboratory data

Five mL of venous blood was collected from patients after overnight fasting in polypropylene tubes. Fresh blood samples were clotted naturally after approximately 1 h at room temperature. Serum was obtained after centrifugation at 4000 rpm for 10 min and stored at −80 °C. FGF21 serum concentration was measured using a commercially available ELISA Kit (Human FGF21 Immunoassay Kit, Antibody and Immunoassay Services, HKU) according to the manufacturer's instructions. Absorbance (at 450 nm) was measured using a microtiter plate reader. Other biochemical parameters such as glucose, lipid profiles, and serum levels of liver and kidney function markers were determined based on photoelectron colorimetric detection principle using Beckman coulter UniCel DxC 600 (Beckman Coulter, Inc.US).

Demographic data of age, gender, and BMI were also collected. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

2.4. Statistical analysis

Normally distributed data were presented as mean ± standard deviation. Data that were not normally distributed were presented as median with interquartile range.

Variables in the study groups were compared using chi-square test, Mann-Whitney U test or unpaired t test, as appropriate. Intrasubject changes from baseline to endpoint for treatment patients' group were evaluated using paired t test or Wilcoxon signed rank test as appropriate. Pearson's correlation or Spearman correlation analysis was used for analyzing the relationship between serum FGF21 levels and other parameters. Linear regression analysis was used to determine the linear relationships between changes in serum FGF21 levels and changes in other clinical values in mania patients over four weeks treatment. Multiple stepwise regression analysis was used to examine parameters independently associated with the change in serum levels of FGF21.

Statistical analyses were performed using IBM SPSS Statistics version 21.0 (Chicago Inc., USA) For each test, p value less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of the bipolar manic and healthy control groups

Characteristics of all subjects in this study are presented in Table 1. We did not find any significant difference between bipolar mania patients and controls subjects in gender and age.

Interestingly, serum glucose (Glu), low-density lipoprotein cholesterol (LDL-C) and apolipoprotein A (ApoA) were significantly lower in mania patients in comparison to those in control subjects (all $p < 0.05$). In contrast, triglycerides (TG) were higher in patients with bipolar manic than in controls but the difference was not statistically significant. As expected, bipolar manic patients had lower concentrations of serum total protein (TP), albumin (ALB), total bilirubin (TBIL), indirect bilirubin (IBIL), and urea compared to the control subjects ($p < 0.05$). In contrast, serum level of uric acid (UA) was markedly increased in bipolar manic patients relative to the healthy controls ($p < 0.001$). No significant difference was observed in cholesterol (CHO), apolipoprotein B (Apo B), high-density lipoprotein cholesterol (HDL-C), alanine amino transferase (ALT), aspartate aminotransferase (AST), γ-glutamyltranspeptidase (γ-GT), alkaline phosphatase (ALP), and creatinine (Cr) between the two groups ($p > 0.05$).

Table 1
Baseline clinical and biochemical characteristics in HC and BD-M groups.

Variables	HC (n = 99)	BD-M (n = 99)	p [a]
M/F	56/43	56/43	–
Age (years)	35.00 (29.00,47.00)	34.00 (26.00,47.00)	–
TG(mmol/L)	0.98 (0.71,1.58)	1.24 (0.76,2.12)	0.109
CHO(mmol/L)	4.99 ± 0.91	4.78 ± 1.15	0.139
HDL-C(mmol/L)	1.32 (1.05,1.47)	1.33 (1.09,1.56)	0.153
LDL-C(mmol/L)	3.22 ± 0.83	2.85 ± 0.91	**0.003**
ApoA(g/L)	1.56 ± 0.23	1.46 ± 0.31	**0.008**
ApoB(g/L)	0.96 ± 0.24	0.94 ± 0.26	0.467
Glu(mmol/L)	5.13 (4.80, 5.56)	4.85 (4.44, 5.41)	**0.005**
TP(g/L)	73.35 ± 3.98	69.2 ± 6.18	<**0.001**
ALB(g/L)	45.68 ± 3.50	41.91 ± 4.25	<**0.001**
TBIL(umol/L)	15.20 (12.60,19.40)	9.70 (7.30,14.20)	<**0.001**
DBIL(umol/L)	2.80 (2.10,3.50)	2.40 (1.70,3.30)	0.087
ALT(U/L)	21.00 (16.00,31.00)	23.00 (15.00,36.00)	0.778
AST(U/L)	22.00 (19.00,26.00)	22.00 (18.00,28.00)	0.561
γ-GT(U/L)	15.00 (12.00,23.00)	16.00 (11.00,27.00)	0.774
ALP(U/L)	66.00 (53.00,82.00)	62.00 (54.00,78.00)	0.701
CREA(umol/L)	77.00 (62.00, 95.00)	76.00 (67.00, 90.00)	0.554
Urea(mmol/L)	5.05 (4.16, 5.91)	3.14 (2.35, 3.93)	<**0.001**
UA(umol/L)	347.00 (265.00, 399.00)	390.00 (333.00, 446.00)	<**0.001**

Data are presented as mean ± SD or median (interquartile range).
Abbreviations: BD-M: patient group with manic episode at baseline; HC: healthy controls. M, male; F, female; TG, triglycerides; CHO, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, lowdensity lipoprotein cholesterol; ApoA, apolipoprotein A; ApoB, apolipoprotein B; Glu,glucose; TP, total protein; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyltranspeptidase; ALP, alkaline phosphatase; CREA, creatinine; UA, uric acid.
[a] p-values of Mann-Whitney U test or Student's unpaired t test.

3.2. Serum level of FGF21 at baseline

Serum level of FGF21 was found to be significantly higher in bipolar manic patients (283.79 pg/mL[162.00, 548.52]) at baseline when compared to control subjects (126.79 pg/mL[78.03, 193.62]) ($p < 0.001$) (Fig. 1a).

We found no significant correlation between FGF21 levels and age and gender in the subjects. However, FGF21 levels positively correlated with serum levels of ApoB ($r = 0.230$, $p = 0.022$) and AST ($r = 0.217$, $p = 0.031$), and negatively correlated with TP ($r = -0.221$, $p = 0.036$) and ALB ($r = -0.363$, $p < 0.001$) in the patients. However, we failed to find significant relationship between baseline FGF21 levels and BMI, TG, CHO, HDL-C, LDL-C, ApoA and Glu in the patients (Table 2).

Table 2
Correlations of serum FGF21 levels with clinical and biochemical characteristics in patient group with manic episode (BD-M) at baseline.

Variables	r	p value
Gender	−0.175	0.082
Age	0.121	0.480
BMI	−0.029	0.777
TG	0.168	0.097
CHO	0.186	0.066
HDL-C	−0.011	0.913
LDL-C	0.116	0.252
ApoA	0.016	0.876
ApoB	0.230	**0.022**
Glu	0.090	0.376
TP	−0.221	**0.036**
ALB	−0.363	<**0.001**
TBIL	−0.028	0.784
DBIL	0.026	0.799
ALT	0.123	0.225
AST	0.217	**0.031**
γ-GT	0.182	0.071
ALP	−0.045	0.661
CREA	0.038	0.710
Urea	−0.128	0.207
UA	0.149	0.141

3.3. Changes in serum levels of FGF21 and biochemical characteristics in bipolar manic patients after 4-week treatment

Data from 82 patients (17 of the original 99 patients were excluded) who completed the follow-up sample, was collected and evaluated. As illustrated in Table 3 & Fig. 1b, serum concentration of FGF21 in manic patients significantly decreased after the treatment, from 279.45pg/mL (151.32,539.12) at baseline to 215.12 pg/mL(103.69,378.49) ($p < 0.0001$), but higher than the controls (126.79 pg/mL[78.03, 193.62]) ($p < 0.0001$, Fig. 1c).

In addition, we found increased serum levels of TG, CHO, LDL-C, Apo-B, Glu, and ALP in these patients. Furthermore, the BMI index in patients was also found to be significantly increased. On the contrary, serum levels of HDL-C, TBIL and DBIL were significantly reduced after

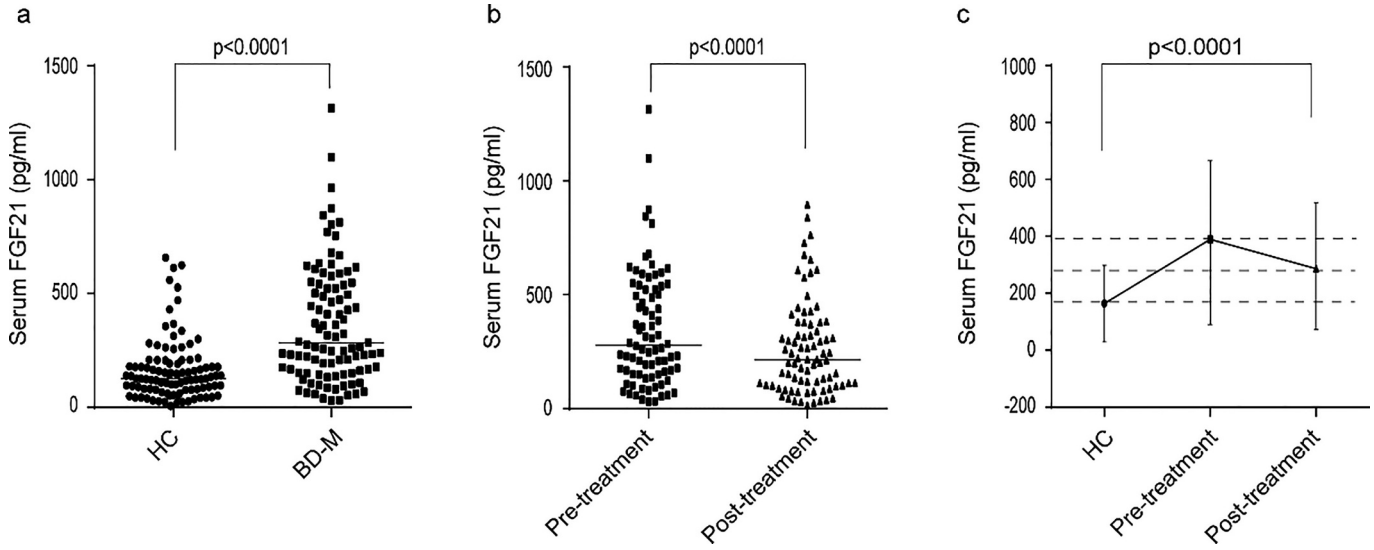

Fig. 1. Serum FGF21 concentrations (pg/ml) in control and bipolar manic subjects. (a) FGF21 levels were significantly higher in BD-M patients compared to HC group, Mann–Whitney *U test* was used. (b) Paired comparison indicated that FGF-21 levels were decreased after 4-week treatment, but (c) still higher than the controls (Mann–Whitney *U test*). BD-M: patient group with manic episode at baseline; HC: healthy controls. Pre- and Post- treatment refer to bipolar manic patients.

Table 3
The change in serum levels of FGF21 and laboratory parameters over four weeks treatment in 82 bipolar mania patients.

Variables	pre- treatment (n = 82)	post- treatment (n = 82)	[a] p^1	Serum Δ FGF21 r	[b] p^2
FGF21 (pg/ml)	279.45 (151.32,539.12)	215.12 (103.69,378.49)	**<0.001**		
BMI (kg/m^2)	23.68 ± 3.52	24.04 ± 3.22	**0.004**	**−0.389**	**<0.001**
TG (mmol/L)	1.13 (0.75,1.63)	1.69 (0.97,2.49)	**<0.001**	**−0.33**	**0.002**
CHO (mmol/L)	4.63 (3.95,5.22)	4.82 (4.05,5.61)	**0.028**	**−0.287**	**0.009**
HDL-C(mmol/L)	1.40 (1.11,1.62)	1.21 (0.96,1.55)	**0.009**	0.161	0.149
LDL-C(mmol/L)	2.61 (2.25,3.30)	2.98 (2.42,3.74)	**0.004**	**−0.327**	**0.003**
ApoA (g/L)	1.49 (1.29,1.65)	1.53 (1.25,1.69)	0.434	−0.007	0. 949
ApoB (g/L)	0.88 (0.73,1.02)	0.92 (0.78,1.08)	**0.034**	**−0.292**	**0.008**
Glu (mmol/L)	4.74 (4.12,5.19)	4.88 (4.51,5.38)	**0.003**	**−0.393**	**<0.001**
TP (g/L)	69.03 ± 6.14	70.10 ± 6.36	0.159	−0.009	0.939
ALB (g/L)	42.20 (39.7, 44.33)	42.40 (38.88,44.63)	0.703	−0.052	0.64
TBIL (umol/L)	10.10(7.85,14.53)	8.55(6.90,11.23)	**0.009**	0.152	0.174
DBIL (umol/L)	2.55 (1.78,3.60)	2.10 (1.70,2.53)	**0.004**	0.112	0.318
ALT (U/L)	21.50 (15.00, 34.00)	23.00 (15.00,37.00)	0.705	0.01	0.928
AST (U/L)	22.00 (17.75,28.00)	22.50 (18.75,29.00)	0.867	−0.09	0.423
γ-GT (U/L)	15.50(5.75, 25.00)	18.00(13.00, 25.00)	0.564	−0.169	0.129
ALP (U/L)	61.00(53.75, 75.25)	66(53.75, 78.75)	**0.043**	−0.04	0.719
CREA (umol/L)	76.5(66.75, 89.25)	78.00(65.75, 95.00)	0.662	0.026	0.818
Urea (mmol/L)	3.05(2.22, 3.89)	3.14(2.37, 4.03)	0.182	−0.149	0.181
UA (umol/L)	392.5(331.50,446.0)	405.00(322.50,472.0)	0.425	0.03	0.788

Data are presented as mean ± SD or median (interquartile range).
p^1: Comparison with baseline and post treatment levels;
p^2: Correlation of the changes in FGF21 level with the changes in metabolic parameters
[a] Paired t test or Wilcoxon signed rank test,
[b] Pearson correlation or Spearman correlation analysis was used as appropriation.

four weeks of treatment (all $p < 0.05$; Table 3). The lower serum FGF21 in response to treatment may contribute to the metabolic disturbance induced by psychotropic drugs.

3.4. Correlation between FGF21 and metabolic parameters in bipolar manic patients after treatment

Correlation between FGF21 and other metabolic parameters in mania patients after four weeks of medication was analyzed (Table 3 & Fig. 2). Changes in serum levels of FGF21 were found to be negatively correlated with the changes in serum levels of TG ($r = -0.33$, $p = 0.002$), CHO ($r = -0.287$, $p = 0.009$), LDL-C ($r = -0.327$, $p = 0.003$), ApoB ($r = -0.292$, $p = 0.008$) and Glu ($r = -0.393$, $p < 0.001$). Furthermore, serum FGF21 levels showed inverse relation with BMI ($r = -0.389$, $p < 0.001$). Multiple stepwise regression analysis showed that changes in BMI, TG, LDL-C and Glu levels were independently associated with changes in serum FGF21 level (Table 4, all $p < 0.05$) .

We found no significant correlation between serum levels of FGF-21 and HDL-C ($r = 0.61$, $p = 0.149$) and ApoA ($r = -0.007$, $p = 0.949$).

At the same time, we found that after 4-weeks of treatment, bipolar manic patients presented with significantly higher NOSIE positive clusters scores including social competence, social interest, personal neatness, and with significantly lower NOSIE negative clusters scores including irritability, manifest psychosis and retardation, in comparison to that before the treatment. In addition, we investigated whether the change in FGF21 level was associated with the treatment outcome in the BD-M patients. We found no correlation between changes in FGF21 level with the changes in NOSIE-30 cluster score and total score (Supplemental Table S2) (all p > 0.05).

4. Discussion

In this study, we analyzed the serum levels of FGF21 in bipolar mania and demonstrated its relationships with metabolic parameters before and after 4 weeks of treatment with psychotropic medication.

The first major finding of this study was that the serum levels of FGF21 were significantly higher in bipolar manic patients in comparison to age- and gender- matched controls, but no correlation was found between levels of serum FGF21 and blood levels of TG, CHO, HDL-C, LDL-C and Glu in manic patients at baseline. According to many reports, FGF21 plays an important role in metabolic regulation and a growing body of evidence suggests that FGF21 plays a role in the brain function (Bookout et al., 2013; Sa-Nguanmoo et al., 2016). In a recent study, FGF21 was found to be expressed in several brain regions (Makela et al., 2014), and administration of FGF21 in D-galactose induced aged mice improved cognitive function (Yu et al., 2015). Furthermore, transgenic mice overexpressing FGF21 showed increased activity in the light environment but decreased activity in the dark environment (Bookout et al., 2013) suggesting an important role of FGF21 on cognition and behavior. In addition, studies have demonstrated that several FGF family members play an important role in psychiatric illness (Evans et al., 2004). Changes in expression of FGFs in psychiatric disorder could be either a cause or effect of the disease. FGF21 has been analyzed in depressed bipolar II disorder patients treated with Valproate (Chang et al., 2018). However, FGF21 has not been studied in bipolar mania. In this study, we found higher serum levels of FGF21 in bipolar manic patients compared to healthy subjects and that the serum FGF21 levels were significantly decreased in the patients after a 4-week treatment with psychotropic medication. We also found that decreased FGF21 levels were associated with the occurrence of multiple metabolic problems which were possibly induced by psychotropic agents. It has been reported that some psychoactive medications cause weight increase, dyslipidemia, hypertension, and impaired glucose tolerance (Filakovic et al., 2012). A recent study reported that FGF21 mRNA and protein expression was elevated following the administration of MS in primary rat brain neurons as well as in neuronal lysates and culture medium presenting a possibility that the deficiency of FGF21 may be an etiologic factor in the development of bipolar disorder (Leng et al., 2015). However, in this study, serum levels of FGF21 were decreased after 4 weeks of APs and MSs co-treatment in mania patients which is in contrast to the study by Leng et al. The possible explanation for this discrepancy may be that the expression of FGF21 in patients may differ from that in rat brain neurons. Moreover, we only detected changes in FGF21 at 4 weeks after the medication and not at the time points used in their study (day 3 and 7).

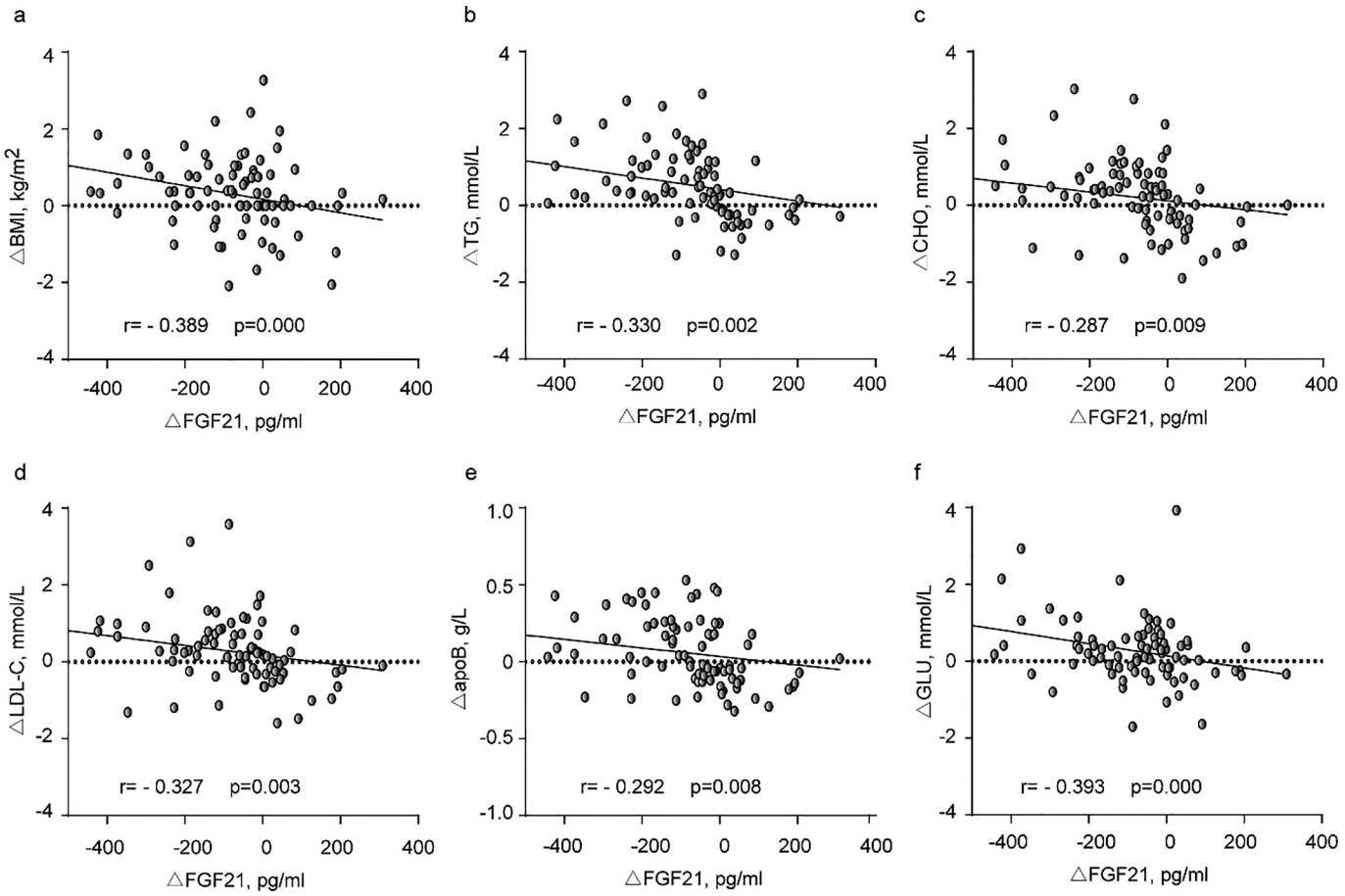

Fig. 2. Relationship of changed serum FGF21 levels with changes of BMI (a), TG (b), CHO (c), LDL-C (d), Apo-B (e) and Glu (f) in bipolar manic patients following treatment. They all showed significantly negative correlations.

Table 4
Multiple stepwise regression analysis showing the variables independently associated with △FGF21 (All $p < 0.05$).

Independent variables	Standardised β	t	p value
△BMI	−0.304	−3.285	0.002
△TG	−0.244	−2.34	0.022
△LDL-C	−0.341	−2.167	0.033
△GLU	−0.342	−3.744	<0.001

Furthermore, as the patients in this study showed reduction in serum FGF21 after receiving treatment with the psychotropic drugs (MSs plus APs), we assume that the observed changes in the levels of FGF21 are most likely caused by the drugs. However, there are no studies that confirmed the effect of APs, particularly the second generation of antipsychotics (SGAs), on FGF21 and warrants further research.

We also found a negative relationship between changes in serum levels of FGF21 and changes in several lipid profiles including TG, CHO, LDL-C, Apo-B, as well as blood glucose and BMI. These findings suggest that a decreased expression of serum FGF21 in response to treatment may contribute to the metabolic disturbance in bipolar manic patients. FGF21 is very effective in lowering glucose, lipids and body weight, but high levels of FGF21 were found in obesity and hyperlipidemia patients (Kharitonenkov and Adams, 2014). This suggests that FGF21 may have a dual role, where at a lower concentration, it has stimulatory effects on metabolism but at a higher physiological concentration, it is associated with metabolic dysfunction.

An interesting finding of this study was the presence of significantly lower levels of Glu, CHO, LDL-C and ApoA levels and no change in the levels of TG, HDL-C and ApoB in manic group at baseline versus control. This finding is inconsistent with what is usually thought of mental disorders as they are more susceptible to metabolic disorders. An explanation is that such findings may be related to the state of the research subjects. For example, in a study evaluating the CHO levels in acute state of BD, significantly lower CHO levels were reported in manic state than in depressive and mixed episodes stages. CHO was suggested to be a stage rather than a trait function (Atmaca et al., 2002; Ghaemi et al., 2000). Notably, our study results showed that the BMI index and serum TG, CHO, LDL-C, Apo-B and Glu levels were significantly increased while the HDL-C concentrations significantly decreased after a short time of psychotropic medication treatment. Thus, attention must be paid to the increasing risks of clinical metabolic disorders that are associated with drug treatment in bipolar disorder patients. More remarkably, the metabolic side effects occurred early with the use of certain psychotropic drugs through modulatory effect on the neural hormone system (Olfson et al., 2006). A lower serum FGF21 may play a role in the progression of metabolic abnormalities possibly induced by psychiatric drugs and may represent a new target for the drug treatment response. In the light of these findings, our future research will focus on investigating whether FGF21 transgenic mice have mental defects and whether the change in FGF21 expression is a causal factor or a consequence of bipolar disorder.

Our study has several limitations. One is the lack of comparative detection of other episodes of BD so we could not determine whether the elevated FGF21 protein level, compared to healthy controls, was characteristic of mania episode. Bipolar disorder subjects with different symptomatology have different severity of metabolic abnormalities (Hsu et al., 2015), A recent study showed that FGF21 level and

metabolic indices do not differ significantly between the controls and depressed bipolar II disorder patients before Valproate teatment (Chang et al., 2018). Therefore, comparative detection of other episodes of BD are needed. Another limitation is the psychotropic dosages in bipolar patients were not discussed in this study. We did not collect detailed information on the administration dosage and the therapeutic drug-level, which may have contributed to the metabolic abnormalities and lipid profile. Since FGF21 may play an important role in the psychopathology of bipolar mania, the severity of the disease may be related to the expression of FGF21. Unfortunately, Young Mania Rating Scale (YMRS) evaluation data (Barbini et al., 1996) was missing in this study and the changes in FGF21 level was not correlated with the change in NOSIE scores. Further studies are needed to evaluate the correlation of BD severity and the levels of serum FGF21. Despite these limitations, our study provides a clue about serum FGF21 levels as a potential biomarker in bipolar mania patients.

Disclosure of interest

The authors report no conflict of interest.

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Supplementary materials

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