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Research Article

Elevated Levels of Visfatin and Fetuin-A in Patients with Major Mental Disorders

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Abstract
A number of cytokines are involved in the regulation of metabolic pathways. The involvement of these metabokines in the pathogenesis of metabolic dysfunction associated with major mental disorders (MMD) is presently poorly understood. **This study therefore,** determined the plasma levels of glucose, fetuin-A and visfatin and their inter-relationship in patients with MMD. Ninety adults consisting of 65 patients with MMD and 25 apparently healthy individuals (controls) were enrolled into this study. After an overnight fast, plasma levels of glucose, visfatin and fetuin-A were determined using the glucose-oxidase method and ELISA as appropriate. Statistical analysis was done using Kruskal Wallis, independent Student's t-test, Mann-Whitney *U* and Spearman's correlation as appropriate. *P*-values less than 0.05 were considered as statistically significant. Patients with MMD had significantly higher levels of fasting plasma glucose (FPG), visfatin and fetuin-A compared with the controls. Fetuin-A had a significant positive correlation with visfatin and FPG in patients with MMD. Comparing the subgroups of MMD with one another, patients with schizophrenia had a significantly higher level of visfatin compared with patients with depression. The plasma levels of fetuin-A were significantly higher in patients with schizophrenia and bipolar compared with patients with depression. It could be concluded from this study that Patients with MMD especially, those with schizophrenia and bipolar disorder have elevated levels of fetuin-A and visfatin suggesting a possible role in the pathogenesis of metabolic dysfunction associated with major mental disorders.

Key Words: *Fetuin-A, Hyperglycaemia, Mental illness, Metabokine, Metabolic dysfunction, Visfatin*

INTRODUCTION

It is apparent that mental illness is a continuum of illnesses affecting not only the brain in which mild to severe disturbances in thought and/or behavior occur but also of metabolic dysfunction which predispose the patients to developing metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM) (Toalson *et al*., 2004; Funk *et al*., 2010; Akinlade *et al*., 2016, 2017). The need to unravel the relationship between psychosis and metabolic dysfunction requires further research as the mechanisms behind this association remain poorly understood (MacKenzie *et al*., 2018). The metabolic alteration is worsened by the use of antipsychotics and it is now clear that metabolic dysfunction is an unfortunate price that patients with major mental disorders (MMD) pay to achieve near optimum mental health (Owashi and Kamijima, 2012). A number of cytokines of different sources regulate important physiological processes and metabolic pathways; these metabokines are thus, implicated in the pathogenesis of insulin resistance (IR), MS, T2DM and cancer (Bluher, 2014; Grolla *et al*. 2016; Aroner *et al*., 2017; Carbone *et al*., 2017). Similarly, there are clinical evidences that cytokines play vital roles in various mental and mood disorders including schizophrenia, depression, eating and sleep disorders, anxiety disorders and some neurodegenerative disorders (Warren *et al*., 2012; Koo *et al*., 2013; Wędrychowicz *et al*., 2014). Some of these cytokines include visfatin and fetuin-A among others.

Visfatin, also known as pre-B-cell colony-enhancing factor (PBEF) or nicotinamide phosphoribosyl transferase (Nampt), is a 52-kilodalton, 491 amino acids containing peptide with autocrine, paracrine and endocrine functions. It is synthesized by the adipose tissue (adipocytes and infiltrating macrophages), skeletal muscle, liver, immune cells, cardiomyocytes and the brain. Its biological activities have been proven beyond cytokine function as it is the enzyme catalyzing the rate-limiting step in the salvage pathway of nicotinamide adenine dinucleotide generation (Adeghate, 2008; Alexiadou *et al*., 2012; Dahl *et al*., 2012; Ekpe and Omotoso, 2017). Visfatin is also believed to be an insulin-mimetic hormone, this report however, remains controversial (Revollo *et al*., 2007). The concentration of visfatin follows a diurnal rhythm, peaking during early afternoon. This rhythmicity is suggested to have a regulatory impact on glucose homeostasis (Benedict *et al*., 2012).

Reports have shown that plasma visfatin concentration is elevated in patients with obesity, type 1 and 2 DM, MS and cardiovascular diseases, and its level is positively associated

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with insulin resistance (IR) (Chang *et al*., 2011, Alexiadou *et al*., 2012; Kocelak *et al*., 2015). Despite a report showing that visfatin reduces hippocampal cell death and improves learning and memory deficit (Erfani *et al*., 2015), there are limited reports on visfatin levels in patients with MMD and the possible effect of antipsychotics on its levels. Dahmen *et al*. (2008) reported that there is elevated visfatin level in narcoleptic patients compared with controls. Also, Basoglu *et al*. (2010) showed that in spite of changes in body mass index, waist circumference, triglyceride, low density lipoprotein-cholesterol, leptin, ghrelin and orexin, visfatin level did not change significantly during six weeks of antipsychotic treatment in first episode male patients with psychosis.

Fetuin-A is another cytokine with important role in metabolism regulation. It is protein product of *AHSG* gene in humans with a key role in the pathophysiology of T2DM as it is considered a physiological inhibitor of insulin signaling (Mathews *et al*., 2000; Aroner *et al*., 2017). Aside its ability to inhibit the insulin action, fetuin-A promotes lipid-induced IR by acting as an endogenous ligand of Toll-like receptor-4 (TLR-4) thereby positioning it as a therapeutic target for managing IR and T2DM (Pal *et al*., 2012; Perez-Sotelo *et al*., 2017). It has been reported that fetuin-A has a significant association with IR (Shidfar *et al*., 2014; Shim *et al*., 2017). Mori *et al*. (2006) showed that patients with T2DM had similar fetuin-A concentration with the controls but there was a significant association between fetuin-A and Homeostasis Model Assessment index of Insulin Resistance (HOMA-IR) in the controls which was not observed in the diabetics. Intriguingly, despite the established implication of fetuin-A in IR pathogenesis, its elevation is associated with better performance on tests of cognitive and executive function in older adults (Laughlin *et al*., 2014). In patients with Alzheimer's disease (AD), Smith *et al*. (2011) reported that fetuin-A concentration was lower compared with controls but had significant positive correlation with MMSE and, an inverse correlation with tumor necrosis factor-alpha (TNF-α). Recently, we (Akinlade *et al*., 2019) reported that patients with major mental illnesses have elevated level of adiponectin which does not appear to be influenced by central adiposity and type of antipsychotic medication. This report, as well as previous reports, highlights the need for more research that would further elucidate the role of metabokines in the course of metabolic dysfunction in mental illnesses. This thus, serves as the basis for this study.

MATERIALS AND METHODS

Study participants

Ninety adults consisting of 65 patients with major mental disorders (MMD) and 25 apparently healthy individuals, who served as controls, were enrolled into this case-control study after Ethical Approval by the Ethics Committee of the University College Hospital, UCH, College of Medicine, Ibadan, Nigeria. Patients with MMD, who were all on antipsychotics, were randomly selected from amongst the patients enrolled at the New World Specialist Hospital, Ibadan, Nigeria into our previous study (Akinlade *et al*., 2016). The anthropometric and clinical characteristics of the study participants have earlier been reported (Akinlade *et al*., 2019). Two participants from the control group were excluded from the study due to abnormally high plasma levels of fasting plasma glucose.

Sample collection

Venous blood was collected from each participant after an overnight fast of about 8 to 10 hours to determine the plasma levels of glucose, visfatin and fetuin-A. All samples were collected between 8.00 am and 9.00 am.

Laboratory analyses

Plasma level of glucose was determined using the glucose oxidase method. One milliliter (1 ml) of glucose reagent was dispensed into each test tube. Thereafter, 10 µl of plasma/standard/control was added appropriately, to each test tube and incubated at room temperature for 20 minutes. Absorbance of each solution was measured spectrophotometrically at a wavelength of 500 nm. The concentration of plasma glucose was calculated as the concentration of standard multiplied by the ratio of absorbance of sample to the absorbance of standard.

The plasma levels of visfatin and fetuin-A were determined using ELISA (WKEA, China) following the manufacturers' instructions. Briefly, the assay is a quantitative sandwich immunoassay technique. A monoclonal antibody specific for visfatin or fetuin-A has been pre-coated onto a 96-well microplate. Visfatin or fetuin-A in the standards, samples and controls is sandwiched by the immobilized antibody and enzyme-labelled polyclonal antibody specific for visfatin or fetuin-A. The enzyme substrate was added, colour developed and after stopping the reaction with an acid, the intensity of the colour developed (which is directly proportional to the concentration of visfatin or fetuin-A) was measured spectrophotometrically.

Statistical analysis

The distribution of the data was assessed using histogram with normal curve. Results are presented as mean ± standard deviation or as median (interquartile range) for Gaussian and non-Gaussian distributed data respectively. Statistical analysis was done using Kruskal Wallis, independent Student's t-test, Mann-Whitney *U* and Spearman's correlation as appropriate. *P*-values less than 0.05 were considered as statistically significant

RESULTS

The median plasma levels of glucose, visfatin and fetuin-A in patients with MMD and controls are shown in Table 1. Patients with MMD had significantly higher levels of FPG, visfatin and fetuin-A compared with the controls.

Comparing the subgroups of MMD with one another and with the controls, the median levels of glucose were similar between the subgroups of MMD but the median levels in patients with schizophrenia and bipolar disorder were significantly higher when compared with the controls. Similarly, the median levels of visfatin and fetuin-A in patients with schizophrenia and bipolar were significantly higher compared with the controls.

Considering the MMD groups, patients with schizophrenia had significantly higher level of visfatin compared with patients with depression. Also, the median levels of fetuin-A were significantly higher in patients with schizophrenia and bipolar compared with patients with depression (Table 2).

Table 1:
Plasma levels of glucose, visfatin and fetuin-A in patients with major mental disorders (MMD) and controls

	MMD (n = 65)	Control (n = 23)	*P*-value
Age (years)	31.70 ± 12.60	27.48 ± 5.71	0.114
FPG (mg/dl)	88.45 (82.18 – 100.69)	85.00 (78.50 – 90.50)	0.026*
Visfatin (µg/L)	28.00 (19.78 – 45.00)	9.56 (7.43 – 15.38)	0.000*
Fetuin-A (ng/ml)	6500.00 (5444.00 – 8159.00)	3767.60 (3119.27 – 5050.83)	0.000*

*Significant at $P<0.05$, FPG = Fasting plasma glucose

Table 2:
Plasma levels of glucose, visfatin and fetuin-A in subgroups of patients with major mental disorders and controls

Parameters	Schizophrenia (n = 35)	Bipolar disorder (n = 20)	Depression (n = 10)	Control (n = 23)	*P*-value
FPG (mg/dl)					
Median	88.70[a]	95.10[a]	84.00	85.00	0.042*
IQR	83.10 – 94.10	78.85 – 104.80	83.35 – 102.30	78.50 – 90.50	
Visfatin (ug/L)					
Median	30.91[a,b]	25.47[a]	14.53	10.91	0.000*
IQR	24.40 – 42.22	10.41 – 51.53	8.17 – 20.68	7.74 – 16.89	
Fetuin-A (ng/ml)					
Median	7217.59[a,b]	6453.64[a,b]	4405.76	3825.25	0.000*
IQR	5774.19 – 8952.30	5606.88 – 8413.94	3498.24 – 6442.5	3124.18 – 5543.56	

*Significant at $P<0.05$, [a]Significantly different from control, [b]Significantly different from depression, FPG = Fasting plasma glucose, IQR = Interquartile range

Table 3:
Correlation between plasma levels of visfatin, fetuin-A and glucose in patients with major mental disorders

	r-value	*P*-value
Visfatin vs Fetuin-A	0.502	0.000*
Visfatin vs FPG	0.183	0.177
Fetuin-A vs FPG	0.314	0.016*

*Significant at $P<0.05$, FPG = Fasting plasma glucose

As shown in Table 3, Fetuin-A had significant positive correlation with Visfatin and FPG. However, there was no significant correlation between Visfatin and FPG.

DISCUSSION

The role of metabokines in the pathogenesis of MMD-associated metabolic disorders is still poorly understood. The observed significantly elevated level of FPG in MMD is in line with the report of Olsson *et al*. (2015). It is well known that altered glucose metabolism is prevalent among individuals with MMD and appears to be integral to MMD (Ohaeri and Akanji, 2011; Alosaimi *et al*., 2017). This association is promoted by multiple factors including genetic and lifestyle factors, the disease itself and treatment with antipsychotics (Balhara, 2011; Olsson *et al*., 2015; Penninx and Lange, 2018). In addition to these factors, our observation could also be due to the elevated level of fetuin-A in MMD compared with the controls. A significant association exists between fetuin-A and IR due to the ability of fetuin-A to inhibit insulin action and promote lipid-induced IR (Pal *et al*., 2012; Shidfar *et al*., 2014; Perez-Sotelo *et al*., 2017; Shim *et al*., 2017). Our observation indicates that there is possible increased release of metabokines favouring IR in patients with MMD. Identification of these metabokines as well as their inducers could be of therapeutic purpose in prevention and management of hyperglycaemia and/or DM in patients with MMD.

The insulin-mimetic property of visfatin remains controversial (Revollo *et al*., 2007). Hammarstedt *et al*. (2006) reported that circulating level of visfatin is approximately 2-fold higher in patients with type 2 diabetes compared with individuals without diabetes. Elevation of plasma visfatin level in patients with MMD as observed in this study could be one of the physiological mechanisms through which elevated glucose level is mitigated in these patients. This is in line with our earlier report (Akinlade *et al*., 2019) showing significant elevation in the plasma level of adiponectin, an adipocytokine whose low level is usually associated with IR, in this group of patients with MMD. The suggested possible hyperglycaemic-mitigating role of visfatin is further buttressed by the significant positive correlation between fetuin-A, visfatin and fasting plasma glucose levels. A number of reports have shown that visfatin level is positively associated with IR (Chang *et al*., 2011; Alexiadou *et al*., 2012; Kocelak *et al*., 2015).

While the association between MMD and metabolic alteration is established, the phenotypic expression of the alteration varies depending on the type of mental illness (Hammarstedt et al., 2006). Akinlade *et al*. (2016) reported that overweight and obesity, which are risk factors for insulin resistance and dysglycaemia, are more prevalent in patients with schizophrenia and bipolar disorder compared with patients with depression. In contrast, fasting plasma insulin as well as indices of insulin sensitivity and β-cell function was shown not to be significantly different when patients with schizophrenia, bipolar disorder and depression were compared with one another (Akinlade et al., 2018). The observed significantly elevated FPG levels in patients with schizophrenia and bipolar compared with the controls could

then mean that dysglycaemia is more associated with schizophrenia and bipolar than depression. This could be responsible for the observed elevated level of fetuin-A and visfatin in patients with schizophrenia and bipolar compared with patients with depression and controls. Variation in the levels of other adipocytokines that are involved in glucose metabolism could be responsible for our observation. Also, differences in psychosocial profile and type of medications could be responsible for our observation. The report of Alosaimi *et al.* (2017) showed that high fasting blood glucose and triglyceride levels are less frequently seen in patients taking the most commonly prescribed antidepressant (selective serotonin reuptake inhibitors) and mood stabilizers respectively. In addition, schizophrenia and bipolar disorder have commonalities in symptoms profile and dopamine blockade (Murray *et al*., 2004).

Small number of patients with depression is a major limitation in this study as it could affect our observations in relation to other groups of major mental disorders. Also, inability to compare the levels of metabokines in drug naïve patients with patients on anti-psychotic drugs is a limitation; following up drug naïve patients through the course of antipsychotic therapy could provide a better understanding of metabokine homeostasis.

It could be concluded from this study that patients with MMD especially, those with schizophrenia and bipolar disorder have elevated levels of fetuin-A and visfatin. Further studies on these metabokines are suggested as they may play some useful roles in the pathogenesis of MMD-associated metabolic dysfunction and could give an insight into possible therapy

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