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*Afr. J. Biomed. Res. Vol. 22 (September, 2019); 235- 239*

*Research Article*

# Effect of Adiposity and Type of Antipsychotic Medication on Plasma Levels of Resistin and Adiponectin in Patients with Major Mental Illnesses

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**ABSTRACT**

Metabolic alteration is not uncommon in patients with major mental illnesses (MMI) and adipokines are thought to play some roles. Presently, the link between adiposity, adipokines release and MMI is still poorly understood. This study was carried out to determine the possible impact of central adiposity and type of antipsychotic medication on plasma levels of adiponectin and resistin in patients with MMI. Plasma levels of adiponectin and resistin were determined in ninety adults comprising 65 patients with MMI and 25 apparently healthy individuals, who served as controls. Anthropometry and blood pressure (BP) of the study participants were taken using standard methods. Anthropometric indices, BP and plasma level of adiponectin, but not resistin, were significantly higher in patients with MMI compared with the controls. The median plasma adiponectin level was significantly higher in patients with depression compared with patients with schizophrenia and the controls. However, the median plasma levels of adiponectin and resistin were insignificantly higher in patients with central obesity compared with patients without central obesity and in patients on atypical drugs compared with patients on typical drugs. Also, there was no significant difference in the median plasma levels of adiponectin and resistin in patients on clozapine or olanzapine compared with those on risperidone. It could be concluded from this study that patients with MMI have elevated level of adiponectin which does not appear to be influenced by central adiposity and type of antipsychotic medication.

**Keywords:** *adiposity, mental illness, resistin, adiponectin*

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*Received: September 2018; Accepted: June, 2019*

***Abstracted by:***
*Bioline International, African Journals online (AJOL), Index Copernicus, African Index Medicus (WHO), Excerpta medica (EMBASE), CAB Abstracts, SCOPUS, Global Health Abstracts, Asian Science Index, Index Veterinarius*

## INTRODUCTION

Adipose tissue, which was viewed as a reservoir for energy, continues to be an important organ involved in regulating lipid metabolism as well as other processes including host defense, inflammation and apoptosis (Liang and dong Ye, 2019). Its products , which could be hormones, cytokines and other inflammatory factors, play important roles in regulating systems within the body and are involved in the pathogenesis of numerous metabolic diseases (Bohler *et al*., 2010).

It is known that metabolic abnormalities are not uncommon in patients with major mental illnesses (MMI) (Akinlade *et al*., 2016) however, the mechanisms underlying the abnormalities are not completely understood. Sequel to the widely established link between adipokines and metabolic alteration in obesity and metabolic syndrome, metabolic alteration associated with MMI can also be potentially mediated by adipokines, among other factors including antipsychotic use, physical inactivity, obesity, psychological stress and genetic predisposition (Taylor and Macqueen, 2010, Expert-Committee, 2013).

One of the prominent and well-studied adipokines is adiponectin which is a 244-amino acid peptide produced by mature adipocytes. Adiponectin is involved in the aetiology of depression-related disorders (Wedrychowicz *et al*., 2014) and its level has been shown not to be low in patients with depression only but also in patients with schizophrenia and panic disorders (Cohn *et al*., 2006, Diniz *et al*., 2012, Unsal *et al*., 2012). Lehto *et al*. (2010) showed that the likelihood of depression increases with approximately 20% with each 5μg/ml decrease in serum adiponectin. Furthermore, Liu *et al*. (2012) reported that adiponectin has antidepressant-like activity and its decreased level is associated with impaired glucocorticoid-mediated negative feedback on hypothalamic-

pituitary-adrenal (HPA) axis. In patients with schizophrenia, Song *et al*. (2013) reported elevated adiponectin level in drug naïve, first episode schizophrenia patients with normal body weight. However, a meta-analysis by Bartoli *et al*. (2015) showed that patients with schizophrenia do not have lower adiponectin level, except those on clozapine and olanzapine, when compared with apparently healthy individuals. These reports show that the mechanisms involved in adipokine level alteration as well as its relation to the pathogenesis of schizophrenia need further research.

Another adipokine of significant importance in metabolic regulation is resistin. Despite the available reports on the association between resistin and insulin resistance (IR), the exact role it plays in the pathogenesis of manifestations of IR such as type 2 diabetes mellitus is still poorly understood (Jamaluddin *et al*., 2012). During inflammation, its level increases with increasing levels of mediators of inflammation thereby making it suitable in predicting severity of certain diseases (Reilly *et al*., 2005, Cherneva *et al*., 2013, Emamalipour *et al*., 2019). There has been conflicting reports on serum resistin levels in patients with major depressive disorder (MDD). Carvalho *et al*. (2014) reported lower resistin level in MDD compared with controls. Similarly, Weber-Hamann *et al*. (2007) reported lower resistin level in patients remitting to anti-depressive treatment compared to non-remitters. In contrast, Pan *et al*. (2008) reported that there is no association between depression and resistin. Although the exact role of resistin in the pathogenesis of bipolar disorder (BD) is not known, it is suggested to be involved in the pathogenesis of the disease (Wedrychowicz *et al*., 2014). Yumru *et al*. (2012) reported elevated resistin level in patients with BD compared with controls. Similarly, resistin level is shown to be elevated in patients with schizophrenia,this was attributed to its proinflammatory property (Klemettila *et al*., 2017).

In order to provide information on the link between adiposity, adipokines, type of antipsychotic medication and mental disorders, this study was carried out to determine the plasma levels of adiponectin and resistin in patients with major mental illnesses.

## MATERIALS AND METHODS

**Selection of Study Participants:** After obtaining an approval from the University of Ibadan/University College Hospital (UI/UCH) Joint Ethical Committee and written informed consent or assent from the participants, relatives or caregivers as appropriate, ninety adults comprising 65 patients with major mental illnesses (MMI) and 25 apparently healthy individuals were enrolled into this study. Participants with MMI were randomly selected from amongst the patients enrolled into our previous study (Akinlade *et al*., 2016). In brief, 124 adult patients with either schizophrenia, depression or bipolar were enrolled into a study on "metabolic alteration in major mental illnesses". Out of this cohort, 90 patients with stable medical condition were carefully selected for this study.

**Diagnosis of Major Mental Illness (MMI)**: Diagnosis of MMI; schizophrenia, depression and bipolar disorder was made using the Structured Clinical Interview for DSM IV Axis I Disorder (SCID) version 2.0. The SCID is used as part of a normal assessment procedure to confirm a particular diagnosis or in research or screening as systematic evaluation of a whole range of medical states (Akinlade *et al*., 2016, 2018).

**Measurement of Anthropometric Indices and blood sample collection:** Anthropometric indices were measured using standard method (Akinlade *et al*., 2016). Venous blood samples were obtained from the study participants after an overnight fast (8 – 10 hours) and plasma obtained appropriately. Samples were kept at -20$^0$C until analyzed.

**Laboratory Analysis:** Plasma levels of adiponectin and resistin were determined using ELISA (WKEA, China) following manufacturer's instruction.

**Statistical Analysis**

Statistical analysis was done using ANOVA, Kruska Wallis, independent Student's t-test and Mann Whitney *U*. *P*-values less than 0.05 were considered as statistically significant.

## RESULTS

Table 1 shows the anthropometric indices, blood pressure and plasma levels of adiponectin and resistin in the study participants. The mean body weight, BMI, WC, HC, SBP and DBP were significantly higher in patients with MMI compared with the controls. Similarly, the median plasma level of adiponectin was significantly higher in patients with MMI compared with controls. However, the median plasma resistin levels were similar between the 2 groups.

**Table 1:**
Anthropometry, blood pressure and plasma adiponectin and resistin in patients with major mental illnesses (MMI) and controls

| Parameters | MMI (n = 65) | Controls (n = 25) | P-value |
|---|---|---|---|
| Height (m) | 1.68 ± 0.10 | 1.69 ± 0.08 | 0.477 |
| Body weight (kg) | 72.10 ± 15.23 | 64.52 ± 9.85 | 0.008* |
| BMI (kg/m$^2$) | 25.64 ± 4.95 | 22.57 ± 3.20 | 0.005* |
| WC (cm) | 87.58 ± 13.52 | 78.28 ± 8.81 | 0.002* |
| HC (cm) | 99.23 ± 12.47 | 87.60 ± 6.92 | 0.000* |
| WHR | 0.89 ± 0.11 | 0.89 ± 0.07 | 0.977 |
| SBP (mmHg) | 114.55 ± 13.53 | 104.60 ± 10.20 | 0.001* |
| DBP (mmHg) | 76.60 ± 11.62 | 69.20 ± 6.40 | 0.003* |
| Adiponectin (mg/l) | 1807.56 (1204.56 – 2557.85) | 1106.63 (877.85 – 2072.73) | 0.015* |
| Resistin (µg/l) | 17.29 (13.13 – 20.91) | 19.37 (14.95 – 21.30) | 0.194 |

**Significant at P<0.05, BMI = Body mass index, WC = Waist circumference, HC = Hip circumference, WHR = Waist hip ratio, SBP = Systolic blood pressure, DBP = Diastolic blood pressure*

**Table 2:**
Waist circumference and plasma levels of adiponectin and resistin in patients with schizophrenia, bipolar, depression and controls

| Parameters | Schizophrenia (n = 35) | Bipolar (n = 20) | Depression (n = 10) | Controls (n = 25) | *P*-value† | *P*-value‡ |
|---|---|---|---|---|---|---|
| WC (cm) | 87.23 ± 13.98[a] | 87.25 ± 13.86 [a] | 89.67 ± 12.10 [a] | 78.28 ± 8.81 | 0.886 | 0.021* |
| Adiponectin (mg/l) | 1431.29 (1153.23– 2409.68) | 1866.87 (1126.22 – 2485.35) | 2423.08 (1766.45 – 2895.75)[a,b] | 1106.63 (877.85 –2072.73) | 0.077 | 0.016* |
| Resistin (µg/l) | 17.33 (12.71 – 25.19) | 17.93 (6.40 – 19.20) | 15.94 (13.24 – 18.56) | 19.37 (14.95 – 21.30) | 0.608 | 0.395 |

**Significant at P<0.05, WC = Waist circumference,† P-value obtained after comparing the schizophrenia, bipolar and depression groups using Kruska Wallis, ‡ P-value obtained after comparing the schizophrenia, bipolar, depression and control groups using Kruskal Wallis, [a]compared with controls, [b]compared with schizophrenia group.*

**Table 3:**
Plasma levels of adiponectin and resistin based on adiposity and type of drugs

| | Adiponectin (mg/l) | Resistin (µg/l) | WC (cm) |
|---|---|---|---|
| **Central adiposity** | | | |
| Normal adiposity (n = 29) | 1422.37 (1139.11 – 2516.05) | 16.76 (5.86 – 20.52) | 77.04 ± 10.05 |
| Central obesity (n = 36) | 1843.18 (1275.09 – 2532.66) | 17.67 (14.27 – 21.11) | 95.78 ± 9.63 |
| P-value | 0.250 | 0.275 | 0.000* |
| **Type of drug** | | | |
| Typical (n = 41) | 1519.20 (1188.78 – 2593.70) | 16.98 (13.13 – 19.59) | 87.33 ± 13.98 |
| Atypical (n = 24) | 1930.35 (1174.63 – 2599.98) | 18.27 (13.85 – 21.24) | 88.27 ± 13.54 |
| P-value | 0.624 | 0.363 | 0.796 |
| **Type of atypical drug** | | | |
| Clozapine & Olanzapine (n = 13) | 1896.24 (1269.89 – 2540.81) | 17.33 (10.14 – 21.29) | 91.85 ± 12.54 |
| Risperidone (n = 11) | 2031.32 (1093.42 – 2637.92) | 18.93 (17.37 – 22.84) | 83.11 ± 13.97 |
| P-value | 0.920 | 0.301 | 0.141 |

**Significant at P<0.05, WC=Waist circumference*

There was progressive increase in the median plasma adiponectin levels from schizophrenia, bipolar through depression. The median plasma adiponectin level was significantly higher in patients with depression compared with patients with schizophrenia and the controls (Table 2). Due to the association between central adiposity and adipokine production, the MMI group was divided into two subgroups viz; normal central adiposity (<80cm for female, <94cm for male) and central obesity (≥80cm for female, ≥94cm for male). The median plasma levels of adiponectin and resistin were insignificantly higher in patients with central obesity compared with patients without central obesity (Table 3). Similarly, the median plasma levels of adiponectin and resistin were insignificantly higher in patients on atypical drugs were compared with patients on typical drugs (Table 3). When patients on atypical drugs were subdivided into those on risperidone and those on clozapine or olanzapine, there was no significant difference in the median plasma levels of adiponectin and resistin when the 2 groups were compared with each other (Table 3).

## DISCUSSION

Metabolic derangements continue to be a prominent feature of major mental illnesses (MMI). The observed elevation in anthropometric indices is not a novel finding. Earlier reports have shown that patients with MMI have increased of overweight and obesity, both central and peripheral (Dickerson *et al*., 2006, Simon *et al*., 2006, Saarni *et al*., 2009, Kivimaki *et al*., 2009). This has been attributed to the illness itself, binge eating, unhealthy lifestyle habits and treatment related factors (McElroy, 2009). These factors could also explain the observed elevation in blood pressure, albeit within the acceptable clinical cut-off, in patients with MMI.

Adiponectin is a circulating adipokine involved in anti-inflammation, modulation of brain functions and sensitization of the body to insulin thereby playing a role in glucose and lipids metabolism (Une *et al*., 2011). The observed significantly elevated level of adiponectin in patients with MMI contradicts the reports of Cohn *et al*. (2006) and Beumer *et al*. (2012) but supports the reports of Song *et al*. (2013) and Bartoli *et al*. (2015). It has been shown that adiponectin inversely correlates with body mass index (BMI), body fat mass and visceral adiposity as larger adipocytes tend to produce lower level of adiponectin (Aprahamian and Sam, 2011, Parida *et al*., 2019). This was not the case in this study as patients with MMI had elevated adiponectin level even with wider waist circumference (WC) and higher BMI than the controls. The observed elevation in adiponectin level might be a physiologic compensatory machinery through which the known metabolic effects of central and peripheral obesity are contained. This could also explain the observed significant elevation in adiponectin level in patients with depression, a group with wider WC, compared with patients with schizophrenia and controls thereby corroborating the report of Liu *et al*. (2012) which showed that adiponectin has antidepressant-like activity. An experimental study by Kim *et al*. (2007) revealed that increased expression of adiponectin

expands subcutaneous adipose tissue which causes resistance to the deleterious impact of high-fat diets on insulin sensitivity via increased expression of peroxisome proliferator-activated receptor gamma(PPAR-γ) target genes and reduction in adipose tissue infiltration by macrophages culminating in reduced systemic inflammation. However, caution is necessary in interpreting adiponectin level as its elevation is identified as an independent risk factor for the development of dementia and Alzheimer disease (van Himbergen *et al*., 2012). Furthermore, its elevation is associated with increased total pericardial fat mass and cardiomyopathy (Kim *et al*., 2007).

The association between atypical antipsychotics and adverse metabolic events is well established although, the mechanisms involved are poorly understood (Richards *et al*., 2006, Savoy *et al*., 2010, Wang *et al*., 2013). Reports have shown that the type of atypical antipsychotics and the duration of usage could have differential effect on plasma adipokine level (Oriot *et al*., 2008, Bai *et al*., 2009, Oral *et al*., 2011, Bartoli *et al*., 2015). The observed insignificant elevation in plasma adiponectin and resistin levels in patients on atypical drugs compared with patients on typical drugs and in those on clozapine and olanzapine compared with those on risperidone suggests that disordered adipokine level in patients with MMI involves several coordinated metabolic processes and not solely dependent on the type of drug used. This assumption is further buttressed by the observed similar levels of plasma adiponectin and resistin in patients with normal adiposity and central obesity despite the significant, but expected, differences in the WC of the two groups. Therefore, adipokine dysregulation might involve myriads of factors working synergistically and not central obesity and use of atypical antipsychotics alone. Further studies especially, with large population size, are suggested to substantiate findings from this study as small sample size was a limitation. Also, the baseline levels of adiponectin and resistin were not determined in patients with MMI before the commencement of antipsychotic medications.

It could be concluded from this study that patients with major mental illnesses have elevated level of adiponectin which does not appear to be influenced by the waist circumference and type of antipsychotic medication.

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