

A cross-sectional evaluation of adiponectin plasma levels in patients with schizophrenia and schizoaffective disorder

Linda Hanssens^a, Ruud van Winkel^{b,c}, Martien Wampers^b, Dominique Van Eyck^b, Andre Scheen^d, Jean-Yves Reginster^a, Julien Collette^e, Joseph Peuskens^b, Marc De Hert^b

^a Department of Epidemiology and Public Health, University Liège, Belgium

^b University Psychiatric Center Catholic University Leuven, Leuvensesteenweg 517, 3070 Kortenberg, Belgium

^c Department of Psychiatry and Neuropsychology, EURON, South Limburg Mental Health Research and Teaching Network, Maastricht University; PO box 616, 6200 MD Maastricht, The Netherlands

^d Department of Diabetology, CHU de Sart Tilman, University Liège, Belgium

^e Department of Clinical Biology, CHU de Sart Tilman, University Liège, Belgium

Abstract:

Background: In recent years, several studies showed increased rates of hyperglycaemia, diabetes, dyslipidemia, metabolic syndrome as well as cardiovascular disease in schizophrenic patients. The underlying mechanism, however, is poorly understood. Adiponectin is a recently identified adipocyte-derived protein, with low adiponectin levels being associated with metabolic abnormalities such as obesity, insulin resistance and type 2 diabetes. **Methods:** Fasting adiponectin levels were assessed in a cross-sectional sample of 386 patients with schizophrenia or schizoaffective disorder. All patients were on monotherapy of second-generation antipsychotics (SGA) and underwent an extensive metabolic screening including an oral glucose tolerance test (OGTT). **Results:** Adiponectin plasma levels were inversely correlated with BMI, and differed significantly between patients with normal weight, overweight or obesity ($p < 0.05$). Patients who met criteria for the metabolic syndrome, according to adapted National Cholesterol Educational Program - Adult Treatment Panel criteria (NCEP-ATP III) (29.3%), had significantly lower adiponectin levels than patients not meeting metabolic syndrome criteria ($p < 0.0001$). Patients without glucose abnormalities (78%) had significantly higher adiponectin levels than patients with diabetes (5.7%) ($p < 0.05$). After controlling for components of metabolic syndrome and sex, antipsychotic medication independently influenced adiponectin levels ($p < 0.0001$), with the lowest mean levels in patients on clozapine and olanzapine. **Conclusions:** Adiponectin levels in schizophrenic patients mirror what is observed in the general population, with the lowest levels in the most metabolically comprised subjects. However, antipsychotic medication may also influence adiponectin regulation independently, a finding that should be confirmed in longitudinal studies.

Keywords: Schizophrenia; Metabolic syndrome; Antipsychotic; Adiponectin; Diabetes

1. Introduction

Over the last years, convincing evidence has been put forward to suggest an increased prevalence of metabolic abnormalities such as diabetes and the metabolic syndrome in patients with schizophrenia (Allison et al., 1999; Homel et al., 2002; Scheen and De Hert, 2005, 2007). An emerging literature suggests an association of certain antipsychotics with the development of metabolic abnormalities (Allison and Casey, 2001; Jin et al., 2004; Dufresne, 2007; Meyer and Koro, 2004; Newcomer, 2005, 2007a,b). These metabolic abnormalities may in turn contribute to the higher risk of cardiovascular disease in patients with schizophrenia (Casey, 2005; De Nayer et al., 2005; Haupt and Newcomer, 2001; Hennekens et al., 2005; Jin et al., 2002, 2004; Newcomer, 2005; Newcomer, 2007a; Scheen and De Hert, 2005, 2007; Tschoner et al., 2007). However, the mechanism underlying antipsychotic-induced metabolic dysregulation is still unclear. Several hypotheses have been suggested, such as appetite stimulation which is linked to the affinity of some SGAs to neurotransmitters involved in food intake, 5HT_{2a} and 2c serotonergic receptors, but also H₁ histaminergic, α 1 and α 2 adrenergic receptors and muscarinic (M₃) receptors (Elman et al., 1999, 2002; Elmquist and Flier, 2004; Kroeze et al., 2003; Newcomer, 2005; Reynolds et al., 2002). In order to understand the underlying mechanisms, Bergman and Ader (2005) and Ader et al. (2005) evaluated the effects of antipsychotics on glucose homeostasis in dogs and found that the hyperinsulinemic compensation was inadequate to counter insulin resistance under olanzapine treatment, although it is unclear whether this was due to a central or peripheral effect.

Changes in insulin sensitivity, potentially induced by deregulated adipocytes are of particular interest with regard to the metabolically deleterious effects of antipsychotic medications. Over the last decade, it became apparent that these cells play an important endocrine role in ensuring normal metabolic homeostasis. They secrete a variety of proteins like resistin, IL-6, TNF alpha, and adiponectin, which affect insulin sensitive organs like the liver and muscles (Sato et al., 2001). Free Fatty Acids (FFA) produced by adipocytes, essentially in presence of abdominal obesity, can induce insulin resistance (Arner, 2001).

In human plasma, circulating adiponectin levels are high (5-30 µg/ml) (Hotta et al., 2000). The protein, also known as adipocyte complement related protein, plays a role in glucose and lipid homeostasis (Hara et al., 2005; Lihn et al., 2005; Guerre-Millo, 2008; Sherer et al., 1995). It decreases the postprandial rise of plasma FFAs and improves post-absorptive insulin suppression of glucose production by the liver. A strong correlation between adiponectin levels and insulin sensitivity has been established (Arita et al., 1999; Berg et al., 2001, 2002; Lihn et al., 2005; Guerre-Millo, 2008). Plasma adiponectin levels are lower in obese than in lean people (Arita et al., 1999; Matsuzawa et al., 2004). The protein is also associated with anti-atherogenic properties, preventing the development of atherosclerotic plaque, by inhibiting TNF alpha production by macrophages (Berg et al., 2002; Matsuzawa et al., 2005a,b). Decreased levels of adiponectin are associated with insulin resistance and hyperinsulinemia (Weyer et al., 2001; Yamauchi et al., 2001). High levels of adiponectin are associated with low risk of developing type 2 diabetes. In non-diabetic patients adiponectin levels are negatively correlated with triglycerides and low levels of adiponectin may accelerate atherosclerosis in patients with dyslipidemia (Matsuda et al., 2002; Matsubara et al., 2002). A recent population based study carried out by Dekker et al., 2008, showed that high levels of adiponectin did predict mortality, in particular in patients with prevalent CVD. The authors hypothesized that adiponectin would protect against metabolic and vascular diseases, but in the study, patients already suffering from CVD, adiponectin was compensatory up-regulated. The metabolic effects of adiponectin are mediated through the activation of 5'Adenosine-Mono-Phosphate-activated-kinase (AMPK). This enzyme also mediates the vascular endothelial cells and the effects on the myocardial muscle through different processes which lead to its protective effects against cardiovascular diseases. Distinct adiponectin receptors, AdipoR1 and AdipoR2 which are unequally distributed in the target tissues, are involved.

In patients with schizophrenia, adiponectin levels were found to correlate with metabolic parameters in clozapine-treated patients in a similar fashion as found in the general population (Bai et al., 2007). However, higher levels of insulin-resistance were found in clozapine-treated patients compared to subjects from the general population matched for BMI and waist, indicating that illness-related or treatment-related factors may further increase insulin resistance in overweight patients with schizophrenia (Wu et al., 2007). A recent study in patients with schizophrenia that focused on the early changes in glucose metabolism after initiation of an atypical antipsychotic suggested that glucose dysregulation may develop as early as within three months after initiation (van Winkel et al., 2008). These dysregulations may involve adipocyte hormones such as adiponectin, as was suggested by a recent study by Bai and colleagues who found that independent of age and BMI, serum adiponectin was a biomarker for the metabolic syndrome in clozapine-treated patients with schizophrenia (Bai et al., 2007). The current study aimed to i) assess plasma adiponectin levels in 386 patients with schizophrenia as a function of metabolic outcomes and ii) assess differential effects of antipsychotic medication on adiponectin levels, controlling for the potentially confounding effects of the individual components of the metabolic syndrome and sex. These confounders were based on previous research in non-psychiatrically ill populations.

2. Methods

In November 2003, a naturalistic screening and monitoring protocol for metabolic abnormalities was initiated and is still ongoing at the university psychiatric hospital and affiliate services of the University Psychiatric Centre Catholic University Leuven. The screening methods have been described in detail elsewhere (De Hert et al., 2006a,b; Van Winkel et al., 2006). In short, referral by the treating psychiatrist for metabolic screening and monitoring is a clinical routine in the hospital and its affiliate services. Antipsychotic drug regimens are recorded and patients are being monitored using fasting laboratory tests, Oral Glucose Tolerance Tests (OGTT) and clinical examinations. Psychiatric diagnoses according to DSM-IV criteria were established by experienced psychiatrists affiliated with the University Centre and responsible for the patient's treatment. Written informed consent was obtained from all patients. The study was approved by the local ethical committee and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice requirements. Patients who were on monotherapy of SGA for at least 6 months were considered for this study. 386 patients, among the assessed patient cohort, with a diagnosis of schizophrenia or schizoaffective disorder, fulfilled this criterion.

All patients had a 75gr glucose load Oral Glucose Tolerance Test (OGTT) and a fasting blood sample taken for the assessment of individual items among the assessed patient cohort of the metabolic syndrome. Blood pressure and waist were assessed during a clinical examination. Patients were initiated on an overnight fast and were monitored during the OGTT.

Plasma samples were centrifuged at 4 °C and frozen at -80 °C. Adiponectin samples were assessed by a solid phase ELISA which contains NSO-expressed recombinant human adiponectin and has shown to accurately quantitate the recombinant factor (B-Bridge International, 2002). The assay employs the quantitative sandwich enzyme immunoassay technique.

The presence of the metabolic syndrome was assessed using the adapted National Cholesterol Educational Program -Adult Treatment Panel (NCEP-ATP III) criteria (fasting glucose ≥ 100 mg/dl plus the inclusion of treatment for hypertension, with lipid lowering medication and/or with antidiabetic medication as criteria) (NCEP, 2001 ; Grundy et al., 2004). For the diagnosis of diabetes and pre-diabetic abnormalities the criteria of the American Diabetes Association were used (Impaired fasting glucose (IFG) ≥ 100 mg/dl and < 125 mg/dl, Impaired Glucose Tolerance (IGT) glucose ≥ 140 mg/dl and < 200 mg/dl at 2 h in the OGTT) (Expert Committee, 2003, 2008)). Markers of β -cell function (HOMA β cell) and insulin resistance (HOMA IR) were calculated using the homeostasis model assessment (HOMA) index algorithm derived from the fasting glucose and insulin concentrations (Matthews et al., 1985).

Descriptive statistics were computed for the basic demographic and clinical variables as well as for the laboratory variables relevant for the evaluation of metabolic abnormalities.

The association between adiponectin level and the individual components of the metabolic syndrome was measured by a Pearson correlation. Independent t-tests were used to evaluate differences in mean adiponectin levels as a function of presence/absence of the metabolic syndrome, gender, elevated triglyceride levels (≥ 150 mg/dl), and low HDL cholesterol levels (male < 40 mg/dl, female < 50 mg/dl). Chi-square tests were used to test the association between antipsychotic treatment and the presence/absence of the metabolic syndrome and the presence/absence of glucose abnormalities.

The effect of BMI category (normal weight, overweight, obese), glucose (diabetes, prediabetes, no abnormalities) and lipid abnormalities on mean adiponectin levels was tested by means of a one-way ANOVA as was the influence of antipsychotic treatment on mean glucose, insulin and adiponectin levels.

An ANCOVA was used to test the effect of antipsychotic treatment on mean adiponectin level when controlling for the individual components of the metabolic syndrome as well as for sex.

3. Results

3.1. Patient baseline demographics characteristics

The sample consisted of 386 patients who were on average 35.9 (STD = 11.8) years old. Their mean duration of illness was 10.5 years (STD = 10) and 64% of patients were male. 99% were Caucasian and Belgian natives. Their mean GAF score was 60.7 (STD = 9.5). They had been admitted to the hospital on average 4.7 times (STD = 4). 24.9% were outpatients at the time of assessment; 26.2% of the patients lived alone, 28.5% with their family, 14.8% with a partner, 12.5% in sheltered housing and 18.1% in residential facilities. The majority of the patients were unemployed (75.9%).

The overall distribution of antipsychotic medication was as follows: 7.8% took amisulpride; 16.6% clozapine, 33.4% olanzapine, 16.1% quetiapine and 25.9% risperidone. On average they received 3 (STD = 1.8) different concomitant treatments. Antipsychotics were combined with anticholinergics (11.7%), antidepressants (40.7%), benzodiazepines (31.3%), mood stabilisers (26.9%) and somatic medication (28.8%); 1.0% of the patients were treated for diabetes, 1.6% of patients received a lipid lowering agent and 12.4% took antihypertensive medication.

Table 1: Metabolic parameters per antipsychotic agent

	Amisulpride <i>n</i> =30 (7.8%)	Clozapine <i>n</i> =65 (16.6%)	Olanzapine <i>n</i> = 129 (33.4%)	Queetiapine <i>n</i> =62 (16.1%)	Risperidone <i>n</i> =100 (25.9%)	P
Clinical measures						
Age (years)	33.1 ± 9.9	35.9 ± 9.8	34.8 ± 11.4	38.8 ± 13.4	36.5 ± 12.8	ns
BMI (kg/m ²)	26.2 ± 4.6	27.7 ± 5.1	25.4 ± 4.2	26.6 ± 6.3	25.8 ± 4.9	0.0438
Waist (cm)	94.1 ± 13.0	99.0 ± 14.4	92.3 ± 11.7	93.6 ± 18.1	93.9 ± 12.5	0.0334
Mean dose (mg)	720 ± 305	296 ± 116	16 ± 7	557 ± 289	5 ± 5	NA
Glucose levels (mg/dl)						
Fasting glucose (mg/dl)	89.9 ± 16.5	92.9 ± 19.8	92.9 ± 19.8	90.3 ± 12.8	90.0 ± 11.5	0.0263
Glucose 2 h (mg/dl)	101.5 ± 60.0	95.9 ± 47.5	95.9 ± 47.5	102.1 ± 48.9	95.3 ± 35.6	ns
Insulin levels (mIU/L)						
Fasting insulin	10.1 ± 5.8	12.6 ± 12.3	11.3 ± 9.4	11.8 ± 11.0	9.34 ± 6.8	ns
Insulin 30 min	81.3 ± 48.4	81.2 ± 56.3	78.3 ± 46.6	71.0 ± 51.3	71.4 ± 52.3	ns
Insulin 60 min	69.8 ± 58.6	107.4 ± 95.2	79.6 ± 52.9	77.2 ± 59.4	82.5 ± 108.6	ns
Insulin 120 min	37.1 ± 30.2	44.0 ± 56.9	42.0 ± 52.7	41.3 ± 47.7	34.2 ± 46.2	ns
Insulin index						
HOMA IR	2.3 ± 105	3.2 ± 3.6	2.9 ± 4.8	2.8 ± 2.9	2.1 ± 1.7	ns
HOMA B%	146.2 ± 78.09	136.7 ± 113.6	148.3 ± 90.6	165.4 ± 142.6	144.8 ± 159.6	ns
Lipid levels (mg/dl)						
Total cholesterol	193.9 ± 38.6	195.2 ± 34.6	195.6 ± 44.3	193.7 ± 38.0	191.1 ± 43.2	ns
Triglycerides	150.7 ± 89.6	172.7 ± 78.5	157.7 ± 101.0	144.8 ± 79.1	146.8 ± 101.2	ns
HDL cholesterol	48.6 ± 17.0	46.1 ± 13.4	48.9 ± 15.0	55.2 ± 14.4	51.6 ± 15.2	0.0080
LDL cholesterol	118.7 ± 37.7	114.3 ± 31.2	117.2 ± 41.3	111.4 ± 35.9	113.2 ± 36.3	ns

(Values mean±SD, ANOVA).

3.2. Metabolic risk factors and abnormalities

Rates of metabolic and cardiovascular risk factors in this population were high: 65% were smoking, 21% had regular alcohol consumption, 28% had a family history of diabetes, 35.2% had a family history of dyslipidemia and 48.7% had a family history of cardiovascular disease.

The mean weight was 78.7 kg (STD = 16.0). The mean BMI was 26.1 kg/m² (STD = 5.0), 44.3% of the patients had a normal BMI, 37.1% were overweight and 18.7% were obese. The prevalence of the metabolic syndrome according to the adapted NCEP-ATP111 was 29.3%.

Furthermore, 5.7% (*n*=22) of patients met criteria for diabetes, another 16.3% (*n*=63) met criteria for pre-diabetes (1FG, 1GT or both). The mean fasting glucose level for the overall sample was 92.3 mg/dl (STD = 15.8 mg/dl) and differed significantly between antipsychotic treatments ($F(4,381) = 2.79, p=0.0263$) whereas no significant differences were observed with regard to glucose levels 2 h into the OGTT (Table 1).

The mean fasting insulin level was 11.0 mIU/L, mean HOMA β cell was 148% (HOMA β cell >100% in 63.7% of patients) and mean HOMA-IR was 2.7 (IR >1 in 83.7% of patients), indicative of β -cell overactivity to compensate for insulin resistance (Table 1). For none of these measures, significant influence of antipsychotic treatment was observed, although, all SGAs were associated with insulin resistance and increased β -cell function.

Mean fasting total cholesterol, triglycerides, and LDL cholesterol levels were similar across the antipsychotic treatments (Table 1.). Only HDL cholesterol differed significantly between antipsychotics ($F(4,381)=3.50, p=0.0080$).

Mean fasting adiponectin levels were 8385 ng/ml (STD = 6016 ng/ml); they were significantly lower in men (7037 ng/ml (STD=4965)) than in women (10538 ng/ml (STD = 6965)) ($p<0.0001, t=-5.26$).

3.3. Adiponectin levels and metabolic outcomes

Plasma adiponectin levels negatively correlated with waist ($r=-0.341, p<0.0001$), triglycerides levels ($r=-0.298, p<0.0001$), systolic blood pressure ($r=-0.119, p<0.0001$) and fasting glucose levels ($r=-0.202, p<0.0001$), whereas a positive correlation was observed with HDL levels ($r=0.404, p<0.0001$). Plasma adiponectin levels were also negatively associated with HOMA-IR ($r=-0.202, p<0.0001$).

Plasma adiponectin levels differed significantly as a function of BMI category ($F(2,383)=20.56, p<0.0001$). Patients with normal BMI had significantly higher adiponectin levels than both overweight and obese patients ($p<0.05$) (Table 2). There were no significant differences between overweight and obese patients. Plasma adiponectin levels were significantly lower in patients with metabolic syndrome, defined with adapted NCEP-ATP-III criteria compared to patients without metabolic syndrome ($p<0.0001, t=-6.61$).

We observed significant differences of the rates of metabolic syndrome between the different antipsychotics ($X^2(4) = 12.2, p<0.05$), with the highest rate in patients taking clozapine (46.1%), followed by 30.6% of patients on quetiapine, 27.0% of patients on risperidone, 26.7% of patients on amisulpride and 22.5% of patients on olanzapine.

Significant differences in mean adiponectin levels were observed as a function of the presence of glucose abnormalities ($F(2,383) = 7.18, p<0.0001$). Plasma adiponectin levels only significantly differed between diabetic and normogly-caemic patients ($p<0.05$). No significant differences were observed between patients presenting a pre-diabetic status and patients with normal glycaemia nor between patients with a pre-diabetic status and those meeting criteria for diabetes. No significant differences were observed in the rates of type 11 diabetes between the different antipsychotics.

Mean adiponectin levels were significantly higher in patients with normal levels of triglycerides compared to those with abnormal levels (≥ 150 mg/dl) ($p<0.0001, t=-6.99$). Mean adiponectin levels were significantly higher in patients with normal levels of HDL ($p<0.0001, t=-5.13$) compared to those with low HDL levels (male <40 mg/dl, female <50 mg/dl).

Table 2: Plasma adiponectin as in function of metabolic abnormalities

BMI			* P
Normal (n=171)	Overweight (n=143)	Obese (n = 72)	<0.0001
10,378±7186	7057±4420	5967±3805	
Glycaemia status			
Normal (n=301)	Prediabetes (n=63)	Diabetes (n=22)	<0.0001
8825±6186	7371±5526	4217±1631	
Elevated triglycerides (>150 mg/dl)			** P
No(n = 234)	Yes (n = 152)		<0.0001
9812±66226	6035±3977		
Low HDL cholesterol (male <40 mg/dl, female <50 mg/dl)			** P
No(n = 263)	Yes (n=123)		<0.0001
9252±6404	6345±4506		
Metabolic syndrome			** P
Adapted NCEP-ATP (n=273)	III No Adapted NCEP	-ATPIII Yes(n=113)	<0.0001
9378±6367	5779±4807		

(Values mean±SD in ng/ml; *ANOVA, **t-test).

3.4. Plasma adiponectin levels as a function of antipsychotic medication

Significant overall differences in mean adiponectin levels were observed as a function of antipsychotic treatment ($F(4,381)=2.93, p=0.0209$), although none of the pair-wise comparisons reached significance. When controlling for individual components of the metabolic syndrome and sex ($F(4,374)=2.43, p=0.472$), the effect of antipsychotic treatment remained significant, with the lowest mean levels in patients on clozapine and olanzapine (Table 3). Statistically significant differences ($p<0.05$) in adiponectin levels were observed between olanzapine and risperidone, and olanzapine and amisulpride. No significant difference was observed between the other agents.

Table 3: Mean adiponectin levels (mean and std in ng/ml) per antipsychotic treatment

	Adiponectin level
Amisulpride (n=30)	9578 ± 6682
Clozapine (n=65)	7802 ± 5083
Olanzapine (n=129)	7091 ± 5805
Quetiapine (n=62)	9504 ± 7292
Risperidone (n=100)	9150 ± 5515

4. Discussion

To our knowledge, this is the first study assessing adiponectin levels in a large sample of schizophrenic patients stable on antipsychotic monotherapy with a well evaluated metabolic status.

Fasting glucose levels were within normal ranges for the majority of the patients as opposed to insulin levels, HOMAIR and HOMA β cell which were, on average elevated for the whole sample, indicating a trend for insulin resistance. These findings are in line with high rates of the metabolic syndrome in this sample.

Adiponectin levels in this population varied in the same way as described in the normal, overweight and obese general population (Arita et al., 1999), with associations between low adiponectin values and overweight and triglyceride levels. Also, adiponectin levels in schizophrenic patients with and without metabolic syndrome as well as with and without diabetes mirrored what is observed in the general population (Cote et al., 2005; Hotta et al., 2000; Matsuzawa et al., 2005a,b).

The most important finding of this study was that, after controlling for components of the metabolic syndrome and sex, the effect of antipsychotic treatment on adiponectin levels was significant. The lowest values were found in patients treated with olanzapine. Adiponectin levels in patients treated with clozapine were not significantly lower compared to the other atypicals, despite clozapine's known poor metabolic profile as reflected in the high rate of the metabolic syndrome in the current sample (46%). The underlying mechanisms remain unclear. However, considering the unfavorable metabolic and vascular profile associated with low adiponectin levels, this may have important physical health implications (Cote et al., 2005; Guerre-Millo, 2008; Lihn et al., 2005).

Only a few and mainly small studies evaluated adiponectin levels in schizophrenia. Togo et al. ($n=33$, Togo et al., 2004) showed that patients undergoing treatment with olanzapine or risperidone had significantly higher adiponectin concentrations than age-matched healthy volunteers, even after controlling for BMI. Adiponectin concentrations decreased with increasing BMI in patients taking olanzapine, while elevated levels were observed in patients taking risperidone, regardless of adiposity. Cohn et al. ($n=9$, 2006) found insulin resistance and increased risk for type 2 diabetes in untreated schizophrenic patients, as well as a tendency for lower fasting adiponectin levels compared to matched healthy volunteers. In a recent publication by Bai et al. (2007), found that independent of age and BMI, hypoadiponectinemia was associated with the majority of the measured metabolic parameters and was a predictive factor for metabolic syndrome in 188 clozapine-treated patients.

Three small, short-term prospective studies did not find evidence for significant changes in adiponectin levels after the initiation of an atypical antipsychotic. In a study of 13 patients started on olanzapine, Hosojima et al. ($n = 13$, 2006) did not find a significant decrease in adiponectin levels after 4 weeks of treatment, which is in line with a 6-month prospective study in 7 patients who were also initiated on olanzapine (Murashita et al., 2005). A study in 24 patients with childhood-onset schizophrenia started on clozapine was unable to show significant

changes in adiponectin levels over a 6 week period (Sporn et al., 2005).

The results of the present study may suggest a possible role of antipsychotic treatment in the variation of adiponectin levels in patients with schizophrenia, which is in agreement with the findings of Togo et al. (2004) where high BMI was associated with low adiponectin levels in olanzapine treated patients and with those of Bai et al. (2007) showing an association of adiponectin levels with metabolic parameters and metabolic syndrome as well as a study by Richards and colleagues who found that patients receiving olanzapine ($n=9$) had significantly lower total serum adiponectin as compared with those on conventional treatment ($n=9$) and 16 healthy sex-, BMI, and age-matched controls (Richards et al., 2006). Nevertheless, the results need to be interpreted with caution. Large prospective studies in patients recently switched/started on antipsychotic medication, preferably with long-term follow-up are needed to better establish a possible role of antipsychotics on adiponectin levels and other hormones influencing metabolic homeostasis.

The current study also has some limitations. First, it is a cross-sectional study and patients were not randomly assigned to treatment arms. Second, we failed to include other parameters, such as visceral fat assessment, dietary habits, physical activity level and other hormones which may play a role such as leptin, ghrelin, TNF- α and IL-6 (Hug and Lodish, 2005; Jin et al., 2008; Meier and Gressner, 2004). Adiponectin together with a large number of other anorexic and orexigenic factors plays a role in metabolic disturbance and CVD risk. Since we have only studied adiponectin levels, this limits the generalizability of our findings.

In conclusion, adiponectin levels in schizophrenic patients mirror what is observed in the general population, with the lowest levels in the most metabolically comprised subjects. Findings from the current study suggest that antipsychotic medication may also influence adiponectin regulation independently, a finding that should be confirmed in longitudinal studies with sufficiently large samples.

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Contributors

Study design: L Hanssens, M De Hert, R van Winkel

Data collection: M De Hert, D Van Eyck

Laboratory analysis: J Collette

Statistics: M Wampers

Writing manuscript: L Hanssens and M De Hert wrote the first draft of the manuscript R van Winkel, M Wampers, D Van Eyck, A Scheen, JY Reginster, J Collette and J Peuskens commented on this first draft and contributed to the subsequent revision.

Conflict of Interest

L Hanssens was an employee of BMS at the time of the study, study is part of PhD curriculum in Public Health and epidemiology at the University of Liège.

R van Winkel has been a consultant for Eli Lilly Lilly and has received honoraria from Eli Lilly and Janssen-Cilag.

M Wampers has no conflicts of interest to disclose relative to the article.

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