Schizophrenia Research 106 (2008) 308–314

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

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ARTICLE INFO

*Article history:*
Received 27 February 2008
Received in revised form 8 September 2008
Accepted 9 September 2008
Available online 18 October 2008

*Keywords:*
Schizophrenia
Metabolic syndrome
Antipsychotic
Adiponectin
Diabetes

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.


## 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

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doi:10.1016/j.schres.2008.09.008

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, 5HT2a and 2c serotoninergic receptors, but also H1 histaminergic, alpha1 and alpha2 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 on 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