



Early insulin resistance predicts weight gain and waist circumference increase in first-episode psychosis – A one year follow-up study

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ABSTRACT

First-episode psychosis (FEP) is associated with weight gain during the first year of treatment, and risk of abdominal obesity is particularly increased. To identify early risk markers of weight gain and abdominal obesity, we investigated baseline metabolic differences in 60 FEP patients and 27 controls, and longitudinal changes during the first year of treatment in patients. Compared to controls at baseline, patients had higher low-density lipoprotein, triglyceride and apolipoprotein B levels, and lower levels of high-density lipoprotein and apolipoprotein A-I but no difference in body mass index or waist circumference. At 12-month follow-up, 60.6% of patients were overweight or obese and 58.8% had abdominal obesity. No significant increase during follow-up was seen in markers of glucose and lipid metabolism or blood pressure, but increase in C-reactive protein between baseline and 12-month follow-up was statistically significant. Weight increase was predicted by baseline insulin resistance and olanzapine use, while increase in waist circumference was predicted by baseline insulin resistance only. In conclusion, insulin resistance may be an early marker of increased vulnerability to weight gain and abdominal obesity in young adults with FEP. Olanzapine should be avoided as a first-line treatment in FEP due to the substantial weight increase it causes. In addition, the increase in the prevalence of overweight and abdominal obesity was accompanied by the emergence of low-grade systemic inflammation.

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1. Introduction

Psychotic disorders are associated with increased risk of obesity, metabolic syndrome and type 2 diabetes (Mitchell et al., 2013). It is unclear to what extent this is related to poor nutrition, sedentary lifestyle, and antipsychotic treatment, or whether some of the alterations might actually reflect core pathophysiology of these disorders (Harris et al., 2013). First reports concerning abnormalities of glucose metabolism in psychosis appeared already before the widespread use of antipsychotics, and drug-naïve first-episode psychosis (FEP) patients show impaired glucose tolerance and insulin resistance (Harris et al., 2013; Spelman et al., 2007; Kirkpatrick et al., 2012). Based on a meta-analysis, drug-naïve FEP patients may also have higher waist–hip ratio

and more intra-abdominal fat compared to healthy controls but no difference in body mass index (BMI) (Foley and Morley, 2011).

During antipsychotic treatment, weight increases markedly during the first weeks and months, and most of the total increase takes place during the first year of treatment (Perez-Iglesias et al., 2014). Most antipsychotics cause weight gain with differing propensity (Foley and Morley, 2011; Leucht et al., 2013). Results on pre-treatment lipid abnormalities remain contradictory, while most antipsychotics cause elevated total and low-density lipoprotein (LDL) cholesterol and triglyceride levels and reduced high-density lipoprotein (HDL) cholesterol levels (Foley and Morley, 2011). Abdominal obesity is the hallmark of dysfunctional adipose tissue (Despres and Lemieux, 2006), and people with schizophrenia are particularly vulnerable to this metabolically unfavorable form of obesity (Saarni et al., 2009).

Weight gain is one of the major reasons for problems in treatment adherence (Velligan et al., 2009). The risk of young people to medication induced somatic comorbidities is especially high and should be minimized (Mitchell et al., 2013). Thus, it is of great interest to identify risk factors for weight gain and increased waist circumference specifically in people with recent onset psychosis. Previous studies on FEP patients suggest that risk factors for clinically significant weight increase during

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treatment include lower BMI, younger age, negative symptoms, and olanzapine treatment, but predictors have not been consistent across studies (Strassnig et al., 2007; Perez-Iglesias et al., 2014) and are inadequate to inform clinical decision on treatment. Also inflammation, which is common in FEP (Miller et al., 2011), may contribute to antipsychotic-induced weight gain (Song et al., 2013). Low-grade inflammation has been associated with weight increase in the general population (Vasunilashorn, 2013). It remains unclear whether the risk factors of weight gain and abdominal obesity in early psychosis differ.

The aim of this study was to identify baseline risk factors for weight gain and waist circumference increase at 12-month follow-up among FEP patients comparing them with healthy controls.

2. Methods and materials

2.1. Clinical study protocol and assessment

The ongoing study started on November 2010. FEP patients (age 18 to 40 years) attaining the first treatment for psychosis were recruited from the catchment area of the Helsinki University Hospital. The inclusion criterion for the study was receiving a score of at least 4 in Unusual thought content or Hallucinations in the Brief Psychiatric Rating Scale – Extended (BPRS-E) (Ventura et al., 1993) and being fluent in Finnish language. Substance-induced psychotic disorders and psychotic disorders due to a general medical condition were excluded. Patients with FEP were assessed three times. Baseline assessment was conducted as soon as the patient had entered treatment and was able to give informed consent according to the treating personnel. Follow-ups were conducted at two and 12 months. Data were also gathered on sociodemographic factors, functioning, medication, somatic illness, substance use, physical activity, diet and smoking, and the interviewer measured weight, height, blood pressure and waist circumference (full description of the assessment methods and variables used in this study is given in Supplementary methods).

Controls, matched by age, sex and region of residence, were identified from the Population Register Center and assessed with the same protocol as the patients. The exclusion criteria for the controls were lifetime history of psychotic disorder, chronic neurological, endocrinological, or cardiovascular diseases, and any condition that prevents Magnetic Resonance Imaging.

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa and by the institutional review boards of the National Institute for Health and Welfare (THL), Helsinki, Finland, and the University of Helsinki. All participants gave a written informed consent.

2.2. Laboratory analytical methods

A fasting blood sample was collected at 8 to 10 am. Serum and plasma samples were immediately aliquoted and stored at -80°C . Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, high sensitive C-reactive protein (hs-CRP), insulin, apolipoprotein A-I (ApoA-I) and B (ApoB) and plasma glucose were measured on Abbott Architect ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA) in the laboratory of the Genomics and Biomarkers Unit at National Institute for Health and Welfare. The laboratory has been accredited by Finnish Accreditation Service and it fulfills the requirements of the standards SFS-EN ISO/IEC 17025:2005. The scope of accreditation covers all analyses. The following methods were used: enzymatic assays for measuring total cholesterol, triglycerides and glucose, homogenous method for direct measurement of HDL cholesterol, ultrasensitive immunoturbidimetric assays for ApoA-I, ApoB and hs-CRP and chemiluminescent microparticle immunoassay (CMIA) for insulin. LDL cholesterol was calculated by the Friedewald formula. The mean intra-assay coefficient of variations (CVs) for total cholesterol,

HDL cholesterol, triglycerides, hs-CRP, insulin ApoA-I, ApoB and glucose were 0.8%, 1.0%, 0.6%, 1.4%, 1.7%, 0.7%, 1.0% and 0.8%, respectively.

We used HOMA index as a measure of insulin resistance, and due to its highly skewed distribution, we categorized it based on the 75th percentile (cut-off value 3.71), as in Sossa et al. (2013).

2.3. Outcome variables

We used weight change and change in waist circumference between the baseline assessment and the 12-month follow-up as the main outcome variables. For descriptive purposes, we also present changes in the prevalences of overweight, obesity, and metabolic syndrome using international criteria (Supplementary Table 1).

2.4. Statistical analysis of clinical data

Because most of the variables were not normally distributed, we calculated descriptive statistics for sociodemographic and clinical measures using tests for non-normally distributed variables. Thus, we used Pearson's χ^2 tests (Fisher exact test) or Mann–Whitney *U*-test to test significance in between-group comparisons, and Spearman's rank order correlations to test correlations. Friedman's ANOVA was used to test differences between baseline, 2-month and 12-month assessments for patients who had measurements available at all time points. McNemar's test and Cochran's *Q* were used for categorical variables. For descriptive purposes, we present all *p*-values significant at the <0.05 level.

To examine which baseline variables were associated with changes in weight or waist circumference, we calculated correlations between continuously or ordinally distributed variables and change in weight and waist circumference using Spearman's rank order correlation. For continuous variables, we tested median change in the respective variables using the Mann–Whitney *U* test. From these analyses, we chose variables that were statistically significantly associated with either weight change or change in waist circumference as independent variables for general linear models performed with PROC GLM in SAS. We checked the assumption of normally distributed residuals with the Shapiro–Wilk test.

3. Results

3.1. Characteristics of the participants

By September 2014, blood sample was available from 60 FEP patients and 27 controls included in the study. At the follow-up points of 2 and 12 months, 43 and 22 blood samples from patients were available (72% and 37% of the initial sample), respectively. At baseline, information on weight was available from 59 patients and 27 control subjects. Since the study is ongoing, 12-month follow-up information on weight and waist circumference became subsequently available from altogether 33 and 34 patients, respectively.

Table 1 presents the study participants' demographic characteristics at baseline. Patients and controls were similar in terms of potential confounding factors, but patients had lower education, were more often unemployed and had more often sedentary lifestyle. Psychiatric diagnoses of the patients are presented in Table 2. At baseline, one patient had been diagnosed with type 1 diabetes mellitus (DM), and another patient with type 2 DM, both were insulin treated. None of the control subjects had been diagnosed with DM. Majority of patients had been prescribed a single antipsychotic ($n = 37$) at baseline. Second generation antipsychotics (SGA) had been prescribed to 90% of patients ($n = 54$), and first generation antipsychotics (FGA) to 13% ($n = 8$) (Table 2). Furthermore, 8% ($n = 5$) were drug-naïve. Median duration of antipsychotic treatment at baseline was 26 days.

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