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Original Article

Blood levels of glucose and insulin and insulin resistance in patients with schizophrenia on clozapine monotherapy

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ABSTRACT

Objective: We tested the hypothesis that fasting blood glucose and insulin levels are higher in schizophrenic subjects on clozapine monotherapy compared with healthy controls and they correlate with anthropometric measurements, laboratory tests and body composition.
Methods: Data for 24 subjects with schizophrenia treated with clozapine and 24 age- and sex-matched healthy volunteers was analyzed.
Results: Patients taking clozapine had higher fasting levels of glucose (103.5 ± 31.6 vs. 87.8 ± 11.7 mg/dL, $z = -2.03$, $p = 0.04$), there was no difference for insulin concentrations and markers of insulin resistance. In the clozapine group glucose levels correlated with clozapine dose ($R = -0.43$, $p = 0.03$), while insulin levels correlated with weight ($R = 0.66$, $p < 0.001$), body mass index ($R = 0.54$, $p = 0.007$), abdominal ($R = 0.53$, $p = 0.007$) and waist ($R = 0.43$, $p = 0.04$) circumference, total body fat ($R = 0.51$, $p = 0.01$), and uric acid levels ($R = 0.50$, $p = 0.01$). In the clozapine group insulin levels were lower in subjects with body mass index <25 kg/m^2 (7.0 ± 3.3 vs. 13.4 ± 8.8 μU/mL, $p = 0.04$) and in subjects without abdominal obesity (6.3 ± 2.4 vs. 13.3 ± 8.6 μU/mL, $p = 0.03$).
Conclusions: We found higher blood glucose levels in subjects taking clozapine and no differences in blood insulin levels between subjects with schizophrenia and controls. Associations between blood insulin levels and abdominal/waist circumferences support the role of abdominal obesity as an important risk factor of insulin resistance.

1. Introduction

Insulin is a hormone, produced by beta cells of the pancreas, and is central to regulating carbohydrate and fat metabolism in the body. Insulin causes cells in the liver, skeletal muscles, and fat tissue to absorb glucose from the blood. Insulin resistance (IR) is a state of impaired glucose metabolism. It results from reduced sensitivity of the target tissues (muscles, adipose tissue, liver) to insulin and may lead to the development of type 2 diabetes, accelerated atherosclerosis, hypertension or polycystic ovarian syndrome. Usually, IR develops as a result of abdominal obesity (increased amount of visceral fat), but may also be a factor contributing to its development (for example, treatment with metformin may reduce body weight [1]). It was also hypothesized that the development of insulin resistance may be an adaptive mechanism preventing weight gain secondary to psychotropic medications [2]. The protective effect of insulin resistance may be based on a reduction of peripheral anabolic effect of insulin and increased level of insulin in the brain, which reduces appetite and increases energy expenditure. However, hyperinsulinemia resulting from insulin resistance may stimulate secretion of testosterone, which promotes the storage of fat in the abdominal adipose tissue and leads to abdominal obesity [3]. The development of insulin resistance occurs in the course of treatment with a number of psychotropic drugs. It is particularly frequent in case of atypical antipsychotics (mainly olanzapine, clozapine, quetiapine, and risperidone) [4]. Various methods are used in order to measure insulin resistance, among which the glucose clamp technique is most precise, but also rarely performed in clinical practice. The homeostasis model assessment of insulin resistance (HOMA-IR) is an alternative to the glucose clamp and the most commonly used surrogate measure of insulin resistance in vivo [5]. A more recent method is the quantitative insulin sensitivity check index (QUICKI) [6].

Clozapine is one of the atypical antipsychotics. It remains an ultimate option for patients with treatment resistant schizophrenia

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[7]. Its high efficacy is combined with very low level of extrapyramidal symptoms and ability to ameliorate tardive dyskinesia. It also has some anti-suicidal properties since researches indicate that mortality from suicide is decreased in current clozapine users [8,9]. However, treatment with clozapine is associated with increased risk of fatal agranulocytosis and has also a very detrimental effect on metabolic profile [4], which may contribute to dramatically increased (two to three times) mortality of schizophrenia patients [10] (although in the large (66,881 patients) study from Finland it was demonstrated that clozapine seems to be associated with a substantially lower mortality than any other antipsychotic [11]). Clozapine has a very distinctive pharmacological profile, which probably underlies its efficacy and side-effects [12] and has a well-established diabetogenic risk [13]. Various mechanisms of its diabetogenic properties are considered: (1) a decreased sensitivity to insulin that is independent of the drug, (2) an increased insulin resistance secondary to the drug, (3) effect of the drug on serotonin receptors, and (4) overuse of insulin due to clozapine-induced weight gain [14].

The present study was undertaken with the purpose to determine whether subjects on monotherapy with clozapine have higher levels of fasting blood glucose and insulin compared with healthy controls. Using these variables, markers of insulin sensitivity were calculated. In order to provide more accurate measurements, biochemical and anthropometric measurements were combined with body composition determined using bioelectric impedance analysis (BIA), which provides accurate measurements of body fat, lean mass and body water [15].

2. Methods

Data for 24 European Caucasian adult in-patients with paranoid schizophrenia (295.30, according to DSM-IV, F20.0 according to ICD-10) was included into the study. Minimum clozapine dose was 100 mg/day, no co-medication with other psychopharmacological or non-psychopharmacological drugs was allowed. We have not assessed severity of schizophrenic symptoms (the majority of patients were in stable condition, with no acute psychosis). Previous treatment with antipsychotics was allowed, but clozapine had to be used as monotherapy for at least 2 months prior to the assessments. We have no data for plasma levels of clozapine. Control group consisted of 24 healthy subjects and was gender- and age-matched with patients in the clozapine group. Health status of the control subjects was determined on the basis of basic physical examination, including vital signs and an interview. We have not monitored level of stress, diet or physical exercise. All study subjects have expressed their written informed consent for participation in this study. The study protocol was approved by the Bioethics Committee.

The blood samples for the chemistry panel were collected between 7 am and 8 am, after ensuring at least 8 h of overnight fasting. The samples were immediately transferred to the central laboratory where they were analyzed. Glucose, lipids, calcium and uric acid levels were measured using a Dirui CS-400 analyzer (Dirui, China). Homocysteine chemiluminescence assessments were performed using an Immulite 2000 analyzer (Siemens, Germany), insulin immunochemistry assessments were performed using a Cobas E411 analyzer (Roche Diagnostics, Switzerland) and albumin levels were assessed using a Cobas Integra 800 analyzer (Roche Diagnostics, Switzerland).

Height was measured with a wall-mounted height measure to the nearest 0.5 cm. Weight was measured with a spring balance that was kept on a firm horizontal surface. Subjects wore light clothing, stood upright without shoes and weight was recorded to the nearest 0.5 kg. Body mass index (BMI) was calculated as body weight in kilogram divided by the height in meter squared (kg/m^2). Waist, abdominal and hip circumference were measured using a non-stretchable fiber measuring tape. Fat mass index (FMI) was calculated as total body fat in kilogram divided by the height in meter squared (kg/m^2) [16].

Metabolic syndrome and abdominal obesity were defined according to International Diabetes Foundation (IDF) criteria [17]. Impaired fasting glucose was defined as fasting plasma glucose $\geq$100 mg/dL. BMI $<$25 kg/m^2, 25–30 kg/m^2 and $\geq$30 kg/m^2 were defined as normal weight, overweight and obesity, respectively. Raised triglycerides (TGA) level $\geq$150 mg/dL and/or total cholesterol (TC) $\geq$200 mg/dL and/or reduced HDL cholesterol level $<$40 mg/dL for men and $<$50 mg/dL for women and/or raised LDL cholesterol level $\geq$135 mg/dL were interpreted as dyslipidemia. Corrected calcium was calculated using the formula: corrected calcium (mg/dL) = measured total calcium (mg/dL) + 0.8 (4.0 − serum albumin [g/dL]). Insulin resistance was estimated from fasting glucose and insulin levels using the homeostasis model assessment, calculated with the formula: HOMA1-IR = (fasting plasma glucose [mg/dL] $\times$ fasting insulin [mU/L])/405. HOMA2-IR index was calculated using a calculator downloaded from http://www.dtu.ox.ac.uk. QUICKI index (lower numbers reflect greater insulin resistance) was calculated using the formula: 1/(log(fasting insulin [mU/L]) + log(fasting plasma glucose [mg/dL])). The normal clinical laboratory range for glucose was 55.0–115.0 mg/dL and for insulin was 2.6–24.9 μU/mL.

Body composition was measured using a Maltron BF-906 Body Fat Analyzer (Maltron, UK), single frequency bioelectrical impedance analyzer to determine resistance and reactance at 50 Hz. Standard operating conditions were observed by a trained operator including preparation of the participant, electrode placement and operation. The measurement using BIA was taken immediately prior to anthropometry measurements with participants lying supine, in a rested state.

Statistical procedures were performed with STATA 13.1 for OS X (StataCorp, College Station, TX, USA). Simple descriptive statistics (means and standard deviations, median ($Q2$), 25%, and 75% quartiles ($Q1$ and $Q3$)) were generated for all continuous variables. For discrete variables number of patients and percentages are given. Inter-group differences were analyzed using Mann–Whitney U test. The difference between proportions was analyzed by Fisher's exact test. Associations were tested by Spearman's correlation coefficient. The significant level was set at $p < 0.05$.

3. Results

For group of patients treated with clozapine the mean age was 38.8 ± 12.6 years and 39.9 ± 12.3 years for the control group; there was no significant difference between the groups in age ($p = 0.62$). In both groups there were 12 men, i.e. half of group, and 12 women. In the clozapine group 12 (half of group) subjects smoked cigarettes and 8 in the control group ($p = 0.38$). The mean duration of monotherapy with clozapine was 131.8 ± 114.3 [$Q1$ = 8.5, $Q2$ = 33.0, $Q3$ = 84.0] months and mean clozapine dose was 341.1 ± 148.6 [$Q1$ = 237.5, $Q2$ = 300.0, $Q3$ = 425.0] mg/day. Detailed results for anthropometric measurements and laboratory tests are shown in Table 1. We have found no inter-group differences for body composition analysis. Detailed results for BIA analysis are shown in Table 2. Lean body mass was higher in men in the whole study sample (60.1 ± 6.4 [$Q1$ = 53.8, $Q2$ = 59.7, $Q3$ = 63.6] vs. 43.8 ± 5.4 kg [$Q1$ = 41.3, $Q2$ = 43.9, $Q3$ = 46.4], $z = -5.74$, $p < 0.001$) and in the clozapine group (59.6 ± 5.7 [$Q1$ = 55.3, $Q2$ = 59.7, $Q3$ = 61.4] vs. 45.3 ± 7.0 kg [$Q1$ = 42.5, $Q2$ = 46.4, $Q3$ = 49.1], $z = -3.93$, $p < 0.001$). Similarly, basal metabolic rate was higher in men in the whole study sample (1707.7 ± 182.3 [$Q1$ = 1567.0, $Q2$ = 1731.0, $Q3$ = 1837.0] vs. 1337.3 ± 138.4 [$Q1$ = 1229.5, $Q2$ = 1380.5, $Q3$ = 1389.0] kg, $z = -5.32$, $p < 0.001$) and in the clozapine group (1701.2 ± 138.2 [$Q1$ = 1582.0,