Homocysteine Levels in Patients with Schizophrenia on Clozapine Monotherapy

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Abstract We tested the hypothesis that homocysteine levels are higher in blood of schizophrenic subjects on clozapine monotherapy than in healthy controls and they correlate with anthropometric measurements, laboratory tests and results of bioimpedance analysis of body composition. Data for 24 subjects with schizophrenia treated with clozapine and 24 age- and sex-matched healthy volunteers was analyzed. Regarding the whole group, homocysteine levels were significantly higher in men (17.0 ± 3.4 vs. 12.1 ± 4.0 μmol/L, p = 0.009). Homocysteine levels correlated with waist circumference (R = 0.58, p = 0.003), waist-to-hip ratio (R = 0.57, p = 0.003), basal metabolic rate (R = 0.48, p = 0.01), lean body mass [kg] (R = 0.53, p = 0.008), body water [L] (R = 0.53, p = 0.008) and triglycerides (R = 0.57, p = 0.003). There were no significant differences of homocysteine levels for impaired fasting glucose, abdominal obesity, obesity/overweight, and dyslipidemia. Homocysteine levels did not correlate with age, treatment duration, clozapine dose, weight, body mass index, abdominal circumference, blood pressure, total body fat, cholesterol, high density lipoproteins, low density lipoproteins, uric acid, calcium, glucose, insulin, homoeostasis model assessment of insulin resistance 1, and homoeostasis model assessment of insulin resistance 2. We did not find significant differences in blood homocysteine levels between subjects with schizophrenia and controls. Association with waist circumference may support homocysteine role as an important cardiovascular risk factor. Association with lean weight may explain why men have higher levels of homocysteine than women.

Keywords Schizophrenia · Homocysteine · Clozapine

Abbreviations

CVD Cardio-vascular disease
BIA Body impedance analysis
BMI Body mass index
WHR Waist-to-hip ratio
SBP Systolic blood pressure
DBP Diastolic blood pressure
TC Total cholesterol
HDL High density lipoproteins
LDL Low density lipoproteins
TGA Triglycerides
FPG Fasting plasma glucose
HOMA1-IR Homoeostasis model assessment of insulin resistance 1
HOMA2-IR Homoeostasis model assessment of insulin resistance 2

Introduction

Homocysteine is an amino-acid produced during demethylation of methionine. High levels of homocysteine in blood are associated with increased risk of cardiovascular disease (CVD) [1]. Patients with schizophrenia may have increased levels of homocysteine [2] and this may add to increased CVD risk due to treatment with antipsychotics [3]. Homocysteine concentration is inversely related to the intake and plasma levels of folate [4], while folate deficiency is common in schizophrenic patients [5]. As it was
Materials and Methods

Data for 24 European Caucasian adult patients with paranoid schizophrenia (295.30, according to DSM-IV) was included into the study. These subjects were on clozapine monotherapy for at least 2 months prior the assessments. Control group was 24 healthy subjects and was gender- and age-matched with patients in the clozapine group. All patients and volunteers included in the study have been informed about aims and methods of the study and expressed their written informed consent for participation in this study. The study protocol was approved by the local Bioethics Committee. There was no financial involvement from the industry.

Laboratory Tests

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).

Impaired fasting glucose was defined as fasting plasma glucose ≥100 mg/dL. BMI <25 kg/m², 25–30 kg/m² and ≥30 kg/m² were defined as normal weight, overweight and obesity, respectively. Raised triglycerides (TGA) level ≥150 mg/dL and/or total cholesterol (TC) ≥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 ≥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 results by homeostasis model assessment, using the formula: HOMA1-IR = (fasting plasma glucose [mg/dL] × insulin [mU/L])/405. HOMA2-IR index was calculated using a calculator downloaded from http://www.dtu.ox.ac.uk.

Anthropometric Assessment

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/m²). Waist, abdominal and hip circumference was measured using a non-stretchable fibre measuring tape.

Body Composition Assessment

Body composition was measured using a Maltron BF-906 body fat analyser (Maltron, UK), single frequency bio-electrical impedance analyser 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 Methods

Statistical procedures were performed with STATA 12.1 for OS X (StataCorp, College Station, Texas, 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 $p < 0.05$.

Results

For group of patients treated with clozapine the mean age was 38.8 ± 12.6 [Q1 = 28.0, Q2 = 38.5, Q3 = 47.5] and 39.9 ± 12.3 [Q1 = 30.5, Q2 = 36.0, Q3 = 52.0] 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, Q2 = 1722.5, Q3 = 1790.0] vs. 1362.7 ± 173.0 [Q1 = 1281.5, Q2 = 1388.5, Q3 = 1465.0] kg, $z = -3.87$, $p < 0.001$).

In the clozapine group fasting homocysteine levels correlated with waist circumference ($R = 0.58$, $p = 0.003$), waist-to-hip ratio ($R = 0.57$, $p = 0.003$), basal metabolic rate ($R = 0.48$, $p = 0.01$), lean body mass ($R = 0.53$, $p = 0.008$), body water [L] ($R = 0.53$, $p = 0.008$) and TGA ($R = 0.57$, $p = 0.003$). Fasting serum homocysteine concentration did not correlate with age ($R = 0.24$, $p = 0.26$), duration of clozapine treatment ($R < 0.01$, $p = 0.98$), clozapine dose ($R = 0.02$, $p = 0.91$), weight ($R = 0.38$, $p = 0.07$), BMI ($R = 0.25$, $p = 0.23$), abdominal circumference ($R = 0.35$, $p = 0.09$), systolic blood pressure ($R = 0.06$, $p = 0.77$), diastolic blood pressure ($R = 0.09$, $p = 0.66$), total body fat [kg] ($R = 0.13$, $p = 0.56$), TC ($R = 0.38$, $p = 0.7$), HDL ($R = -0.38$, $p = 0.06$), LDL ($R = 0.39$, $p = 0.06$), uric acid ($R = 0.29$, $p = 0.17$), corrected calcium ($R = -0.12$, $p = 0.57$), glucose ($R = -0.07$, $p = 0.76$), insulin ($R = 0.04$, $p = 0.83$), HOMA1-IR ($R = -0.16$, $p = 0.45$), HOMA2-IR ($R = -0.01$, $p = 0.97$).

The normal clinical laboratory range for homocysteine was 5.0–12.0 μmol/L. There was no difference of fasting homocysteine concentrations between clozapine and control group (14.5 ± 4.4 [Q1 = 11.3, Q2 = 15.5, Q3 = 17.7] vs. 13.6 ± 5.0 [Q1 = 10.2, Q2 = 13.5, Q3 = 16.5] μmol/L, $p = 0.48$). In the clozapine group homocysteine levels were significantly higher in men than in women (17.0 ± 3.4 [Q1 = 15.4, Q2 = 17.2, Q3 = 18.5] vs. 12.1 ± 4.0 [Q1 = 8.1, Q2 = 11.9, Q3 = 15.5] μmol/L, $z = -2.63$, $p = 0.009$). The difference between men and women was also significant for the whole study population (16.5 ± 3.4 [Q1 = 14.0, Q2 = 17.0, Q3 = 18.2] vs. 11.6 ± 4.6 [Q1 = 8.1, Q2 = 11.8, Q3 = 14.4] μmol/L, $z = -3.69$, $p < 0.001$). Blood homocysteine levels were not significantly different between men with schizophrenia and healthy men (17.0 ± 3.4 [Q1 = 15.4, Q2 = 17.2, Q3 = 18.5] vs. 16.0 ± 3.5 [Q1 = 11.8, Q2 = 13.7, Q3 = 14.4] μmol/L, $p = 0.4$) and between women with schizophrenia and healthy women (12.1 ± 4.0 [Q1 = 8.1, Q2 = 11.9, Q3 = 15.5] vs. 11.2 ± 5.2 [Q1 = 8.0, Q2 = 10.6, Q3 = 13.2] μmol/L, $p = 0.6$). In the clozapine group there were no significant differences between smokers and
Table 1 Results of anthropometric measurements and laboratory tests

| Measure                          | Clozapine (n = 24) | Control (n = 24) | p   |
|----------------------------------|--------------------|-----------------|-----|
| BMI (kg/m²)                      | 27.1 ± 3.6 (25.1, 26.2, 30.7) | 24.8 ± 3.5 (22.8, 24.8, 26.8) | z = -2.16 |
| Abdominal circumference (cm)     | 96.5 ± 9.4 (89.0, 97.0, 103.5) | 85.5 ± 11.6 (79.5, 86.0, 93.0) | z = -3.37 |
| Waist circumference (cm)         | 91.1 ± 12.1 (82.5, 90.5, 100.5) | 82.4 ± 10.6 (75.0, 83.0, 89.5) | p < 0.001 |
| WHR                              | 0.92 ± 0.08 (0.87, 0.92, 0.98) | 0.86 ± 0.08 (0.79, 0.86, 0.90) | p = 2.55 |
| SBP (mm Hg)                      | 121.7 ± 13.6 (114.5, 123.5, 129.5) | 136.7 ± 17.9 (123.5, 138.5, 151.5) | p = 0.003 |
| DBP (mm Hg)                      | 81.2 ± 8.5 (75.5, 80.0, 86.0) | 82.8 ± 12.1 (73.5, 83.5, 89.5) | p = 0.60 |
| Homocysteine (µmol/L)            | 14.5 ± 4.4 (11.3, 15.5, 17.7) | 13.6 ± 5.0 (10.2, 13.5, 16.5) | p = 0.48 |
| TC (mg/dL)                       | 194.2 ± 53.2 (157.2, 184.4, 214.6) | 216.6 ± 65.3 (174.3, 205.8, 238.1) | p = 0.17 |
| HDL (mg/dL)                      | 43.5 ± 12.6 (35.0, 39.9, 53.3) | 55.1 ± 14.3 (46.3, 57.1, 64.6) | z = 2.69 |
| LDL (mg/dL)                      | 122.6 ± 41.9 (90.9, 115.4, 154.8) | 128.3 ± 39.7 (94.6, 123.4, 167.3) | p = 0.59 |
| TGA (mg/dL)                      | 140.3 ± 120.4 (74.8, 105.1, 182.6) | 104.3 ± 81.4 (57.1, 85.4, 127.6) | p = 0.19 |
| FPG (mg/dL)                      | 103.5 ± 31.7 (87.4, 94.8, 112.9) | 87.8 ± 11.7 (81.2, 85.9, 95.9) | z = -2.03 |
| Insulin (µg/mL)                  | 11.8 ± 8.2 (6.7, 8.7, 12.3) | 7.7 ± 3.2 (5.6, 7.0, 9.0) | p = 0.08 |
| HOMA1-IR                         | 3.3 ± 3.4 (1.5, 2.0, 3.7) | 1.7 ± 0.8 (1.2, 1.6, 2.1) | p = 0.06 |
| HOMA2-IR                         | 1.6 ± 1.1 (0.9, 1.0, 1.7) | 1.0 ± 0.4 (0.7, 0.9, 1.2) | p = 0.06 |
| Albumin (g/dL)                   | 4.5 ± 0.5 (4.3, 4.5, 4.9) | 4.7 ± 0.3 (4.5, 4.6, 4.8) | p = 0.20 |
| Total calcium (mg/dL)            | 9.0 ± 0.8 (8.5, 9.0, 9.6) | 9.3 ± 0.7 (8.7, 9.3, 9.7) | p = 0.39 |
| Corrected calcium (mg/dL)        | 8.6 ± 0.9 (8.0, 8.7, 9.4) | 8.7 ± 0.7 (8.3, 8.7, 9.3) | p = 0.94 |
| Uric acid (mg/dL)                | 4.5 ± 1.4 (3.5, 4.2, 5.0) | 4.3 ± 1.3 (3.8, 4.4, 4.9) | p = 0.86 |

Data given as mean ± standard deviation (25 % quartile, median, 75 % quartile)

BMI body mass index, WHR waist-to-hip ratio, SBP systolic blood pressure, DBP diastolic blood pressure, TC total cholesterol, HDL high density lipoproteins, LDL low density lipoproteins, TGA triglycerides, FPG fasting plasma glucose, HOMA1-IR homeostasis model assessment of insulin resistance 1, HOMA2-IR homeostasis model assessment of insulin resistance 2

non-smokers (13.6 ± 4.8 [Q1 = 9.0, Q2 = 14.2, Q3 = 16.7] vs. 15.5 ± 3.9 [Q1 = 11.9, Q2 = 16.2, Q3 = 18.5] µmol/L, p = 0.21), subjects with normal and impaired fasting glucose (14.9 ± 4.6 [Q1 = 11.5, Q2 = 15.3, Q3 = 16.2] vs. 14.1 ± 4.53 [Q1 = 8.2, Q2 = 16.8, Q3 = 18.2] µmol/L, p = 0.98), subjects with total body fat lower and higher than target maximum based on BIA (14.4 ± 4.3 [Q1 = 10.7, Q2 = 15.7, Q3 = 17.7] vs. 15.2 ± 5.4 [Q1 = 11.4, Q2 = 13.4, Q3 = 19.0] µmol/L, p = 0.93), subjects with BMI <25 and ≥25 kg/m² (13.6 ± 5.2 [Q1 = 11.5, Q2 = 12.4, Q3 = 15.2] vs. 14.8 ± 4.2 [Q1 = 11.2, Q2 = 15.9, Q3 = 18.2] µmol/L, p = 0.93), without abdominal obesity and with abdominal obesity (15.4 ± 4.2 [Q1 = 11.6, Q2 = 15.7, Q3 = 18.2] vs. 12.4 ± 4.3 [Q1 = 8.2, Q2 = 12.2, Q3 = 16.2] µmol/L, p = 0.19), without and with dyslipidemia (12.6 ± 5.0 [Q1 = 8.2, Q2 = 11.5, Q3 = 15.3] vs. 15.7 ± 3.7 [Q1 = 13.3, Q2 = 16.2, Q3 = 18.3] µmol/L, p = 0.08). No such differences were also found for the whole study group.
Contrary to other observations [2], we did not find that subjects with schizophrenia on clozapine monotherapy had higher fasting homocysteine levels comparing to age- and sex-matched healthy controls. However, using two-sample mean-comparison calculator we have found that homocysteine levels in men were not significantly different than reported by Levine et al. (16.3 ± 11.8 µmol/L; p = 0.42) [21] and significantly higher then reported by Henderson et al. (7.69 ± 1.42 µmol/L; t_{21} = -14.06, p < 0.001) [22]. It should be noted that subjects in the study of Henderson et al. had schizophrenia or schizoaffective disorder and were taking clozapine, risperidone or olanzapine as monotherapy. No details for antipsychotic treatment were given by Levine et al. in their paper. Therefore, we may assume that homocysteine levels in our patients were relatively high, particularly in men. Considering atherogenic properties of homocysteine, this is important since in many cases treatment with clozapine is associated with metabolic side-effects significantly increasing the risk of cardiovascular events. We have confirmed previous observations that fasting homocysteine levels are higher in men than in women, both in the clozapine group, as well as in the whole study population. It was previously reported by Sanchez-Margalet et al. [23] that obese subjects have higher levels of homocysteine. We have found no such associations for abdominal obesity, general obesity (determined using BMI-based cut-off values) and in subjects with total body fat higher than target maximum calculated using BIA. Homocysteine levels were positively correlated with waist circumference and WHR, but not with BMI. Considering the association between hyperhomocysteinemia and raised risk of CVD, this observation is consistent with previous reports that WHR is the best predictor of CVD risk, premature death, stroke, non-insulin-dependent diabetes mellitus and female carcinomas [24], while BMI is negatively correlated to cardiovascular disease, premature death, and stroke, but positively to diabetes [25]. Lin et al. [26] has shown that in male patients with coronary artery disease homocysteine levels are strongly associated with WHR, but not with BMI. Association between homocysteine and TGA blood levels also indicates a potential impact of homocysteine on CVD risk.

### Table 2 Results of body composition analysis

|                          | Clozapine (n = 24) | Control (n = 24) | P   |
|--------------------------|--------------------|-----------------|-----|
| Total body fat (%)       | 32.6 ± 8.4         | 28.9 ± 7.1      | p = 0.06 |
| (29.0, 33.2, 38.5)       | (24.2, 28.9, 33.0) |
| Total body fat (kg)      | 25.6 ± 8.8         | 22.4 ± 8.7      | p = 0.12 |
| (20.1, 24.5, 31.5)       | (18.3, 21.2, 26.2) |
| Target body fat min (%)  | 21.6 ± 4.0         | 22.2 ± 3.6      | p = 0.57 |
| (20.0, 20.0, 24.0)       | (19.0, 22.5, 25.0) |
| Target body fat max (%)  | 27.6 ± 4.0         | 28.2 ± 3.6      | p = 0.57 |
| (26.0, 26.0, 30.0)       | (25.0, 28.5, 31.0) |
| Basal metabolic rate (kcal/day) | 1,532.0 ± 230.9    | 1,513.0 ± 265.4 | p = 0.39 |
| (1,388.5, 1,527.0, 1,722.5) | (1,347.0, 1,386.5, 1,731.5) |
| Target weight min (kg)   | 58.0 ± 9.1         | 56.6 ± 10.1     | p = 0.29 |
| (53.5, 58.0, 64.0)       | (49.0, 53.0, 66.0) |
| Target weight max (kg)   | 69.0 ± 10.3        | 67.9 ± 11.2     | p = 0.41 |
| (64.5, 69.0, 74.0)       | (59.5, 63.5, 78.0) |
| Lean body weight (kg)    | 52.5 ± 9.6         | 51.4 ± 10.8     | p = 0.48 |
| (61.5, 66.8, 70.9)       | (67.0, 71.0, 75.8) |
| Lean body weight (%)     | 67.6 ± 8.1         | 71.1 ± 7.1      | p = 0.07 |
| (46.4, 53.0, 59.7)       | (42.5, 47.7, 61.0) |
| Total body water (L)     | 38.4 ± 7.0         | 37.7 ± 7.9      | p = 0.48 |
| (33.9, 38.8, 43.7)       | (31.1, 34.9, 44.6) |
| Total body water (%)     | 49.9 ± 5.4         | 52.1 ± 5.2      | p = 0.09 |
| (46.5, 48.9, 52.0)       | (49.0, 52.0, 55.5) |
| Target body water min (%)| 50.7 ± 3.2         | 50.1 ± 2.9      | p = 0.57 |
| (49.0, 52.0, 52.0)       | (48.0, 50.0, 53.0) |
| Target body water max (%)| 57.7 ± 3.2         | 57.3 ± 2.8      | p = 0.66 |
| (56.0, 59.0, 59.0)       | (55.0, 57.0, 60.0) |

Data given as mean ± standard deviation (25 % quartile, median, 75 % quartile)
In our study fasting homocysteine levels were positively correlated with lean body mass and body water. Similar results were previously reported for healthy subjects by Battezzati et al. [27]. Several mechanisms explaining this association were proposed (e.g. amount of fat-free mass determines creatine synthesis, which is the single quantitatively most important biological reaction requiring methyl groups from methionine to produce homocysteine or the fact that the level of creatine, whose production is related to fat-free mass, is positively related to the homocysteine concentration). We have found that both in the clozapine group and in the whole study population men had higher amount of lean body mass, which may explain why homocysteine levels are higher in men. The same reasoning could be used to explain observed association between homocysteine levels and basal metabolic rate, since it was also significantly higher in men than in women.

Finally, apart from TGA, we have found no other associations of homocysteine blood levels with any biochemical variable analyzed. Contrary to Henderson et al. [22], we also have found no differences between subjects with normal and impaired fasting blood glucose. However, we were not able to stratify our study sample by folate intake or levels, which was done by these authors. Since they found that folate effects may differ depending on fasting glucose status, we cannot exclude that different folate levels in our subjects could have resulted in the absence of such association. Our observations are similar to previously reported by Abbasi et al. [28], who found no relationship between insulin resistance and plasma homocysteine concentrations in a group of healthy volunteers.

Conclusions

There was no significant difference in blood homocysteine levels between patients wit schizophrenia treated with clozapine and mentally healthy controls. Men with schizophrenia taking clozapine had a significantly higher homocysteine levels than women. Homocysteine levels were positively correlated with waist circumference, WHR, TGA levels, basal metabolic rate, lean weight and body water.

Low number of study subjects limited the probability of finding inter-group differences due to lack of statistical power. Due to the cross-sectional study design causal relationships cannot be established and effect of previous antipsychotic treatment cannot be excluded. Dual-energy X-ray absorptiometry (DXA) could be used to measure body composition and percentage of fat more accurately.

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