Metabolic syndrome and serum homocysteine in patients with bipolar disorder and schizophrenia treated with SGA

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Abstract

There is an accumulating evidence for an increased prevalence of metabolic syndrome (MetS) in bipolar patients which is comparable to the prevalence of MetS in patients with schizophrenia. Hyperhomocysteinemia has emerged as an independent and graded risk factor for the development of cardiovascular disease (CVD) which is at the same time, the primary clinical outcome of MetS. The aim of this study was to ascertain if the presence of MetS was associated with hyperhomocysteinemia in patients with bipolar disorder (N=36) and schizophrenia (N=46) treated with second generation antipsychotics (SGA). MetS was defined according to NCEP ATP-III criteria and the cut-off point for hyperhomocysteinemia was set up at 15 μmol/L. Results of the study indicated that the presence of the MetS is statistically significantly associated with the elevated serum homocysteine in all participants. Since hyperhomocysteinemia has emerged as an independent risk factor for psychiatric disorder and CVD, it could be useful to include fasting homocysteine

serum determination in diagnostic panels of psychiatric patients in order to obtain a better assessment of their metabolic risk profile.

Key words: bipolar disorder; schizophrenia; homocysteine; metabolic syndrome; cardiovascular diseases

1. Introduction

There is an accumulating evidence for an increased prevalence of metabolic syndrome (MetS) or its modal subcomponents in bipolar patients (Fagiollini et al., 2005; Cardenas et al., 2008; Vuksan-Ćusa et al., 2009) which is comparable to (Birkenaes et al., 2007; Corell et al., 2008), or even higher (Kilbourne et al., 2007) than the prevalence of MetS in patients with schizophrenia. Homocysteine is non-protein amino acid that occurs in human by the demetilation of nutritional methionine, catalyzed by methyltransferases (Reif et al., 2005).

There are different genetic-nutrient interactions that can predispose an individual to hyperhomocysteinemia (Cortese and Motti, 2001; Carmel et al., 2003).

Most cases of mild hyperhomocysteinemia are due to the nutritional folate and vitamin B12 deficiency and/or reduced glomerular filtration rate, while in severe cases mutations in key enzyme of homocysteine metabolism-methylentetrahydrofolatreductase (MTHFR) can be found (Feng et al.,2009). It is well known that several widely used drugs, such as lipid-lowering drugs (like fibrates and niacin) or oral hypoglycemic drugs (like metformin), insulin, drugs used in rheumatoid arthritis (corticosteroids and non-steroidal antinflammatory drugs) and anticonvulsants (carbamazepine, phenytoin, phenobarbital) can cause elevated homocysteine concentrations (Dierkes and Westphal, 2005).

Hyperhomocysteinemia has emerged as an independent and graded risk factor for the development of cardiovascular disease (CVD) (Mangoni and Jackson, 2002) which is, at the same time, the primary clinical outcome of the MetS (Ninomiya et al., 2004). Elevated level of serum homocysteine is a risk factor for several diseases of central nervous system (Herrman et al., 2007; Stanger et al., 2009). Hyperhomocysteinemia has been found in young male schizophrenia patients (Levine et al., 2005) and bipolar

patients showing functional and cognitive deterioration (Osher et al., 2004, Dittman et al., 2007, Dittman et al., 2008). The role of elevated levels of homocysteine in psychotic disorders could be explained with partial antagonism on NMDA-glycine site (Neeman et al., 2005), which may contribute to symptom development. Further more, some authors (Gilbody et al., 2007; Ozbek et al., 2008) emphasized that high homocysteine and low folate and vitamin B12 levels may be independent risk factors for development of schizophrenia and bipolar disorder and that folate supplementation could possibly play a protective role in the development of schizophrenia and bipolar disorder when taken during pregnancy.

The association between homocysteine levels and MetS in psychiatric patients is not well characterized. Previous study (Garcin et al., 2006) showed that hyperhomocysteinemia is not associated with the MetS in non-psychiatric male population, but it is weakly correlated with systolic and diastolic blood pressure, creatinine clearance, tobacco use, cholesterolemia, tryglycerides and free fatty acids. On the other hand, results from recent studies confirmed association between MetS (and/or hyperlipidaemia, especially low HDL-c) and hyperhomocysteinemia in patients with CVD showing that MetS and hyperhomocysteinemia could work together in increasing CVD risk (Bellia et al., 2007; Obeid and Herrman, 2007).

The aim of this study was to ascertain if the presence of MetS was associated with hyperhomocysteinemia in patients with bipolar disorder and schizophrenia.

Additionally we investigated if there were differences in the prevalence of metabolic syndrome and homocysteine levels in patients with bipolar disorder and schizophrenia treated with SGA.

2. Methods

2.1. Sample

Subjects were consecutively admitted inpatients with bipolar disorder (N=36, 20 males and 16 females) and schizophrenia (N=43, 30 males and 16 females) treated with SGA at the Department of Psychiatry, University Hospital Centre Zagreb during the period of 36 months.

The diagnosis of bipolar disorder and schizophrenia was made according to diagnostic criteria of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), (WHO, 1996).

Intensity of depressive symptoms in bipolar patients was assessed by Hamilton Depression Rating Scale, HDRS-17 (Hamilton, 1960), while manic symptoms were assessed by Young Mania Rating Scale, YMRS (Young et al., 1978). The intensity of psychotic symptoms of schizophrenia patients was assessed by PANSS (Kay et al., 1987). All bipolar patients who entered the study were in at least one month euthymic phase defined with HAMD-17 score 7 or less and YMRS score 5 or less in order to eliminate the possible influence of the depressive or manic episode on serum homocysteine levels and metabolic parameters. The most recent episode in 19 bipolar patients was manic and in 17 patients was depressive episode. All patients with schizophrenia were in a stable phase which means that pharmacotherapy was not changed within a month. A trained psychiatrist performed clinical evaluation. 89% of bipolar patients and 22% of schizophrenia patients were concomitantly treated with mood stabilizers.

The exclusion criteria were: hypertension, diabetes mellitus, inherited disorders of lipoprotein metabolism, diagnosis of substance abuse, including alcoholism, eating disorder, epilepsy, organic brain syndrome, pregnancy, lactation and use of B-vitamins and carbamazepine.

Written informed consent was obtained from all participants, under procedures approved by the Local Ethics Committee and in accordance with the Helsinki Declaration.

2.2. Assessment

Venipuncture was performed for all subjects between 8 and 9 a.m. after 12 hours overnight fast. Immediately after collecting blood samples, serum concentration of total cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglycerides and serum glucose were determined using enzyme methods and commercial kits (Olympus Diagnostic, GmbH, Hamburg, Germany) on Olympus AU 600 automated analyzer. Inter- assay laboratory coefficients of variation were 3.2% for cholesterol, 2.5 for triglycerides and 3.0% for HDL- cholesterol. Reference intervals for the measured parameters were as follows: cholesterol <5.0 mmol /L, LDL <3.0 mmol /L, HDL>1.0 mmol/L, triglycerides <1.7 mmol/L and glucose >6.1 mmol/L. Total homocysteine serum levels were determined using capillary gas chromatography-mass spectrometry (Stabler et al., 1987). The cut-off point for homocysteine elevation was set at 15 μ mol/L according to the reference of our laboratory and the data from the literature (Hirsch et al., 2004; To-Figueras et al., 2010). Since it is documented that erythrocytes continue to produce and export homocysteine into the plasma after the venipuncture (Calam et al., 2005) the collected specimens are placed in tubes containing EDTA, kept on on ice and centrifuged

within one hour after collecting the blood in order to avoid artifactual increase of homocysteine.

Height and weight of each patient were recorded while they were standing barefoot in light clothes on the medical scale that measures height and weight. Body mass index (BMI) was calculated that body weight in kilograms was divided with squared height value in meters. Waist circumference, which is considered an accurate estimate of visceral adiposity, was measured at minimal respiration at high point of the iliac crest and at the level of umbilicus. Sitting blood pressure was measured in subjects after they were interviewed in the sitting position for about 5 min while discussing neutral topics.

MetS was defined according to NCEP ATP III criteria (Expert panel JAMA, 2001). The presence of 3 or more of the following criteria was required to meet criteria for MetS:

1. abdominal obesity:waist circumference >102 cm in men and >88 in woman
2. hypertrigliceridemia :≥1.7 mmol/L
3. low HDL-cholesterol:<1.04 mmol/L in men and <1.29mmol/L in woman;
4. high blood pressure:≥ 135/85 mm Hg;
5. high fasting glucose:≥6.1 mmol/L

2.3. Data analysis

Baseline characteristics were compared by t-test for independent samples or nonparametric Mann-Whitney test when variable was not normally distributed, when comparing 2 groups. For categorical variables chi-square test was used, or Fisher's exact test for 2x2 contingency tables. As measures of association between variables Contingency coefficient for categorical and Spearman coefficient of correlation for

continuous asymmetrically distributed variables were used. Analyses were done using SPSS for Windows Version 13.0. Probability level of $p<0.05$ was considered to be statistically significant.

3. Results

Results of the study showing differences in demographic, biological and clinical parameters between bipolar disorder and schizophrenia patients are presented in Table 1 and Table 2.

For bipolar patients mean HAMD-17 score was 5.7±1.1, mean YMRS score 4.1±1.7, and mean PANSS score for patients with schizophrenia was 68±15.19.

In our whole sample (BAP+sch) 27(34.2%) patients had MetS.

Regarding gender effect on the prevalence of MetS results indicated that there were no difference between male and female in a whole sample ($\chi^2=3.134$, $p=0.089$, $df=1$).

Results of the study showed higher proportions of hyperhomocysteinemia in males in both groups (35% M, 17% F in bipolar group, 29% M, 20% F in schizophrenia group), but without reaching statistical significance.

Presence of the MetS is statistically significantly associated with the elevated serum homocysteine in all participants (Mann Whitney U = 484.500, $p<0.001$). 67% participants in whole sample with hyperhomocysteinemia had fulfilled criteria for MetS, while only 23% participants without hyperhomocysteinemia had MetS ($p<0.001$). When bipolar and schizophrenia group are taken separately, there is statistically significant association within both groups ($r=0.40$, $p=0.005$; $r=0.36$, $p=0.021$) respectively.

Serum homocysteine significantly correlated with systolic ($r=0.30$, $p<0.01$) and diastolic blood pressure ($r=0.25$, $p<0.05$) in all participants. Looking at bipolar and

schizophrenia patients separately, this association between homocysteine and systolic (r=0.30), as well for diastolic pressure (r=0.27) remained statistically significant (for both $p<0.05$). There were no significant correlations between other subcomponents of MetS and serum homocysteine.

4. Disscusion

Although in the past years more attention has been devoted to the medical burden suffered by patients with schizophrenia, recently similar concern has arisen for bipolar disorder patients. Our results showed that the prevalence of MetS in bipolar disorder (31%) is comparable to the prevalence of MetS in schizophrenia (37%), thus confirming the results from the study of Corell et al. (2008). These findings suggest a shared susceptibility of psychiatric patients to metabolic dysregulations that is not primarily related to specific psychiatric diagnosis.

Knowing that MetS represents a major risk factor for the development of CVD, gender differences in this syndrome may contribute to gender differences in CVD. In recent years, MetS has been more prevalent in men than in women (Regitz-Zagrosek et al., 2010), although other authors found that MetS affects Caucasian men and women roughly equally (Gupta and Gupta, 2010). Prevalence is increasing in general and this increase has been steeper in woman, particularly in young woman during the last decade (Regitz-Zagrosek et al., 2006), where it is mainly driven by obesity. In our sample we did not discover gender differences in the prevalence of MetS in patients with bipolar disorder and schizophrenia which is in line with the results from the study of Bobes et al., (2010).

The mean homocysteine level for schizophrenia patients in our study was 11.1±5.1μmol/l which was very similar to the results (11.6±5.8) from the study of Reif et al., (2005). For our bipolar patients mean homocysteinemia was

14.0±11.9μmol/l which was somewhat higher than in above mentioned study (12.9±3.8μmol/l), possibly because the examined group in that study consisted of bipolar and unipolar depressive patients. As it can be seen, there is a trend of higher homocysteine level in affective disorder than in schizophrenia, although our results did not reach statistical significance. However, it is noteworthy that, in our study, mean values of serum homocysteine in both groups were lower than 15 μmol /L which is a cut-off point for hyperhomocysteinemia.

In contrast to previous studies (Applebaum et al., 2004; Levine et al., 2002, 2005; Reif et al., 2005) in which homocysteine level was found to be higher in males, we could not detect gender-specific differences for homocysteine in patients with bipolar disorder and schizophrenia.

Since 67% participants with elevated serum homocysteine levels had fulfilled criteria for MetS and only 23% participants with normal levels of serum homocysteine levels had MetS we can hypothesize that elevated serum homocysteine levels could be associated with metabolic impairments typically observed in MetS. Previous studies showed inconsistent results regarding association between MetS and hyperhomocyteinemia in relation with CVD (Garcin et al., 2006; Bellia et al., 2007). In the second study authors found co-existence of hyperhomocysteinemia and metabolic syndrome in 67.2% CVD patients suggesting that the presence of two conditions gives rise to stronger increase in CVD risk.

To our knowledge, this is the first study examining the association between MetS and homocysteine levels in psychiatric patients. Previous studies explored homocysteine and some metabolic parameters, but not the complete syndrome. The study from Assies and al. (2004) found an association between omega 6-fatty acids and homocysteine levels in patients with major depression. Another study showed

significant correlation between homocysteine levels and BMI, triglycerides and HDL in patients with schizophrenia (Akanji et al., 2007).

Since our results suggest association between hyperhomocysteinemia and MetS in bipolar and schizophrenia patient, they can indicate the usefulness of including fasting homocysteinemia determination in diagnostic panels of psychiatric patients in order to obtain better assessments of their metabolic risk profile. These findings emphasize the need to develop strategies for controlling the MetS and its components as well as homocysteine levels. Since most cases of mild hyperhomocysteinemia is due to the nutritional folate and vitamin B12 deficiency, this could be of significant clinical importance because most studies showed that vitamin B supplementation can lower homocysteine levels (Lonn et al., 2006; Herrmann et al., 2007).

Limitations of the study regard to small sample size, lack of healthy controls and its cross-sectional design does not allow causal relations. Due to small sample results are only preliminary and further investigations are needed. Also, there was no data on physical activity, smoking, coffee consumption and dietary habits (daily intake of folate and vitamin B12) which may all influence homocysteinemia. We did not measure vitamin B12 and folate serum levels and these measurements should be included in future studies. It is important to note that our patients were not drug free since many drugs can cause homocysteine elevation.The findings from the literature regarding the role of SGA in homocysteine levels are scarce and conflicting. It has been reported that psychotic patients treated with SGA had higher homocysteine than healthy controls and that antipsychotic medication type had no significant effect on absolute levels of homocysteine (Neeman et al., 2005), but the results from another study (Sarandol et al., 2007) showed no differences in homocysteine levels between theese two groups.Bipolar patients were significantly older than patients with

schizophrenia, probably due to the the delay in diagnosing, which could also influence the results since homocysteine levels and the risk of MetS increase with age.

In conclusion, our results suggest strong association between hyperhomocisteinemia and MetS in patients with psychotic disorders. It could be useful to include fasting homocysteinemia determination in diagnostic panels of psychiatric patients in order to obtain a better assessment of their metabolic risk profile.

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