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Hyperhomocysteinemia in Treatment with Atypical Antipsychotics is Independent of Metabolic Syndrome

Atipik Antipsikotiklerle Tedavi Sürecinde Görülen Hiperhomosisteinemi Metabolik Sendromdan Bağımsızdır

Emre Sarandöl[1], Meral Demirci Akgün[1], Aslı Sarandöl[1], Esma Sürmen Gür[1]

[1]Bursa Uludağ University, Bursa

ABSTRACT

Strong association between homocysteine (Hcy) and metabolic syndrome (MetS) is documented in individuals with schizophrenia and it is suggested that alterations in Hcy levels might be secondary to metabolic changes induced by atypical antipsychotics (AA). Serum paraoxonase (PON-1) activity, which is negatively affected by increased Hcy concentrations are lower in schizophrenia, and this may impact the development of metabolic side effects. Forty-five subjects with schizophrenia and 43 healthy volunteers, matched according to age, gender, smoking habits, and MetS predictors, were enrolled in this study to examine how Hcy level, PON-1 activity, and MetS indicators influence each other in schizophrenic individuals on AA treatment. Serum Hcy concentrations were significantly higher (15 ± 8 μmol/L vs 12 ± 3 μmol/L), and PON activity tended to be impaired (182±82 U/L vs 216 ± 110 U/L) in schizophrenia. Serum Hcy concentrations were not different between subjects with and without metabolic syndrome in study (14±4 μmol/L and 16±9 μmol/L) and control groups (12±3 μmol/L and 13±7 μmol/L), respectively. Similarly, PON and aryl esterase (AE) activities were not different between subjects with and without metabolic syndrome in study (PON: 185±100 U/L and 181±76 U/L; AE: 84±34 kU/L and 89±20 kU/L) and control (PON: 215±111 U/L and 216±113 U/L; AE: 83±27 kU/L and 88±33 kU/L) groups, respectively. . Hcy levels and MetS predictors were not statistically correlated. Results indicate that schizophrenic subjects on AA treatment have increased levels of Hcy compared to healthy controls and this is not influenced by the presence of MetS.

Keywords: Atypical antipsychotics, schizophrenia, homocysteine, metabolic syndrome

ÖZ

Şizofreni olgularında homosistein (Hcy) ve metabolik sendrom (MetS) arasında güçlü ilişki olduğu bildirilmiş ve Hcy düzeylerindeki artışın atipik antipsikotikler (AA) ile uyarılan metabolik değişikliklere bağlı gelişebileceği düşünülmüştür. Artmış Hcy düzeylerinin negatif yönde etkilediği serum paraoksanaz (PON-1) aktivitesi, şizofrenili bireylerde düşük bulunmaktadır ve bu durumun metabolik yan etkilere neden olabileceği öne sürülmektedir. Bu çalışmada, AA tedavisi alan şizofreni kişilerde Hcy düzeyleri, PON-1 activitesi ve MetS indikatörlerinin birbirlerinden nasıl etkilendiğini incelemek üzere yaş, cinsiyet, sigara alışkanlığı ve MetS göstergelerine göre eşleştirilmiş 45 şizofreni olgusu ve 43 sağlıklı kontrol ile çalışıldı. Şizofreni olgularında serum Hcy düzeyleri anlamlı olarak yüksek (15 ± 8 μmol/L ve 12 ± 3 μmol/L) bulunurken, PON aktivitesinde (182±82 U/L ve 216 ± 110 U/L) azalma eğilimi olduğu gözlendi. Metabolik sendromu olan ve olmayan bireylerin Hcy konsantrasyonları arasında fark yoktu (Şizofreni grubunda sırasıyla, 14±4 μmol/L ve 16±9 μmol/L; Kontrol grubunda sırasıyla, 12±3 μmol/L and 13±7 μmol/L). Benzer şekilde, PON ve aril esteraz (AE) aktiviteleri değerlendirildiğinde metabolik sendromu olan ve olmayan şizofreni grubundaki bireylerin (PON: sırasıyla, 185±100 U/L ve 181±76 U/L; AE: sırasıyla, 84±34 kU/L ve 89±20 kU/L) ve kontrol grubundaki bireylerin (PON: sırasıyla, 215±111 U/L ve 216±113 U/L; AE: sırasıyla, 83±27 kU/L ve 88±33 kU/L) enzim aktivitelerinde fark bulunmadı.Hcy düzeyleri ile MetS göstergeleri arasında istatistiksel ilişki saptanmadı. Sonuçlara göre, AA tedavisi alan şizofreni olgularında Hcy düzeyleri sağlıklı kontrollere göre daha yüksektir ve bu durum MetS varlığından etkilenmemektedir.

Anahtar sözcükler: Atipik antipsikotikler, şizofreni, homosistein, metabolik sendrom

Address for Correspondence: Emre Sarandöl, Bursa Uludag University Faculty of Medicine Department of Biochemistry, Bursa, Türkiye **E-mail:** sarandol@uludag.edu.tr
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Introduction

Schizophrenia is a severe psychiatric disorder characterized by chronic progressive impairments of physical, cognitive, and psychosocial function. As stated by World Health Organization, schizophrenia, with a prevalence of 0.45% among adults, affects an average of 24 million people worldwide (World Health Organization 2022). People with schizophrenia have a reduced life expectancy compared to the general population, and increased mortality is predominantly due to cardiovascular diseases (CVD). People with schizophrenia have nearly twice the average risk of dying from CVD compared to the general population (Hennekens et al. 2005, Brown et al. 2000). Therefore, studies on the mechanisms that trigger the development of CVD in schizophrenia are of great value. Dyslipidemia, abdominal obesity, hypertension, and hyperglycemia are the major risk factors for CVD and the cluster of these risk factors constitute metabolic syndrome (MetS).

Beyond the traditional risk factors, hyperhomocysteinemia (HHcy) is proposed as a new risk factor of CVD (Obradovic et al. 2018). HHcy is defined as Homocysteine (Hcy) level of greater than 15 μmol/L. Homocysteine, a nonproteinogenic amino acid, is produced by demethylation of methionine, and some metabolic disturbances, nutritional deficiencies, medications for common medical conditions, or genetic polymorphisms may increase the blood Hcy level (Numata et al. 2015, Fe'li et al. 2020). On the other hand, high plasma/serum Hcy levels are reported in schizophrenia and, moreover, are held responsible for schizophrenia (Muntjewerff et al. 2006, Nishi et al. 2014). Muntjewerff et al. (2006) found that a 5-μmol/L increase in Hcy levels increased the risk of schizophrenia by up to 70 %. Evidence of a causal relationship between the plasma total homocysteine and schizophrenia is provided by a Mendelian randomization approach (Numata et al. 2015). Therefore, increased serum levels of Hcy can be considered an independent risk factor for developing CVD in schizophrenia. Apart from this, Vuksan-Ćusa et al. (2011) documented a strong association between HHcy and MetS in subjects with schizophrenia, and Esteghamati et al. (2014) suggested that HHcy and MetS may interact for the occurrence of CVD.

However, discordant results were reported on the association of HHcy with MetS in people with schizophrenia: While Huang et al. (2020) stated that Hcy levels were negatively associated with BMI in schizophrenic individuals, Wysokinski et al. (2013) found that Hcy levels were positively associated with waist circumference and waist-hip ratio but not with BMI. In their study, Misiak et al. (2014) observed that treatment with atypical antipsychotics (AA) caused a significant elevation in Hcy levels in schizophrenic subjects, who also exhibited increased BMI. They also reported that changes in Hcy levels were related to baseline metabolic parameters of the subjects and that MetS or its single components were associated with Hcy levels. They concluded that alterations in Hcy levels might be secondary to metabolic changes induced by AA (Misiak et al. 2014). The conflicting outcomes on the relationship between Hcy levels and MetS indicators show that this subject needs to be further studied (Huang et al. 2020).

Human serum paraoxonase-1 (PON-1) is an HDL-bound esterase synthesized by the liver, which has both paraoxonase (PON) and arylesterase (AE) activities and takes an important place in preventing lipoproteins from peroxidation (Suematsu et al. 2019). PON activity provides hydrolysis of organophosphate compounds such as paraoxon, and AE activity provides hydrolysis of carboxylic esters such as phenylacetate. These PON and AE activities establish the antioxidant property of PON-1 and protect against CVD development (Kennedy et al. 2013). Anti-atherogenic and cardio-protective effects of PON-1 are well described (Karabina et al. 2005). Reduced serum PON-1 activity has been reported in patients with stable coronary artery disease, post-myocardial infarction patients, and patients at increased CVD risk (Granér et al. 2006). The inverse association between PON-1 activity and CVD risk is approved by many investigators (Kunutsor et al. 2016). Apart from this, serum PON-1 activity is negatively affected by increased Hcy concentrations. Hcy is rapidly auto-oxidized to form homocystin mixed disulfides and homocysteine thiolactone in the plasma (Andersson et al. 1995). Increased homocysteine thiolactone affects the biological activity of various proteins by reacting with the Lys amino acids in their structure; in this way, elevated homocysteine thiolactone levels cause depression in PON-1 activity (Ferretti et al. 2003).

Research on PON-1 activity in schizophrenia has gained acceleration recently. Currently, that PON-1 activity is reduced in drug naïve first episode schizophrenia, is broadly approved (Moreira et al. 2019). In an earlier work, our group demonstrated that PON-1 activities were lower in schizophrenic individuals (Sarandol et al. 2007). According to the results of the aforementioned study, it is concluded that people with schizophrenia might have an increased risk for coronary artery disease related to reduced serum paraoxonase activity. Later, Ünsal et al. (2013) observed that PON-1 activity and HDL-C concentration were reduced in schizophrenics on olanzapine treatment and suggested that reduced PON-1 activity might impact the development of metabolic side effects.

How alterations in Hcy level, PON-1 activity, and MetS indicators influence each other in schizophrenia has not reached a final consensus yet. In the present study, we planned to evaluate how Hcy levels and PON-1 activity change in schizophrenic subjects on AA treatment in the presence and absence of MetS.

Method

Sample

Individuals who applied to Uludag University School of Medicine, Department of Psychiatry, Psychosis Outpatient Clinic, between December 2007 and August 2008 were evaluated for the present cross-sectional study. During the study period 126 subjects that had been followed with the diagnosis of schizophrenia, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, APA 1994), were assessed. Among them, subjects that were aged between 18-65 years and were on AA treatment for at least three months were included in the study. The exclusion criteria were having treatment for diabetes mellitus or hypertension, having a history of myocardial infarction, cerebrovascular accident, malignancies, or renal or liver disease. Thirty three subjects that were older than 65 years, 23 subjects that were diagnosed with atherosclerotic cardio vascular disease, 17 subjects that were having treatment for diabetes mellitus and/or hypertension, and 8 subjects that were on AA treatment for less than 3 months were not included in the study.

To detect an effect size of 0.60 (determined by a pilot study), for the difference between serum Hcy levels in subjects and controls, with a power of 80%, at a significance level of 5%, the sample size was estimated as minimum 43 subjects in each group. Forty-five individuals that met the study criteria constituted the study group. Forty-three healthy volunteers, matched according to age, gender, smoking habits, and MetS predictors, were recruited as controls. Individuals having a first-degree relative with a psychiatric disorder, having treatment for diabetes mellitus or hypertension, diagnosed with cardiac or cerebral disorders, having any neurological symptoms, liver or renal failure, or malignancies were not included in the control group.

Procedure

All subjects were evaluated according to the ATP-III (AHA) criteria (Grundy et al. 2005), and a diagnosis of metabolic syndrome was made accordingly. After they were informed about the study procedures, the subjects gave written consent to participate in the study. This study was approved by the Ethics Committee of Uludag University (Date: 04.12.2007; No:2007-23) and was in accordance with the guidelines of the 2002 Declaration of Helsinki. All subjects were examined by two independent specialists in psychiatry, screened for any major health problems, and questioned about their smoking status; body weight, height, waist and hip circumferences, and blood pressure measurements were recorded. As stated in the Quality Management System Documents in our institution (http://sakurdok.uludag.edu.tr/dosya.htm), information confidentiality (PR-ENY-05) and the reliability of all kinds of documents and files of the psychiatry department (PR-ENY-07) are guaranteed by authorizing certain departments and individuals.

Biochemical Analysis

Blood samples were taken following 10-hour fasting; sera were portioned for PON and AE activity measurements and were stored at -80°C until analyzed. The remaining sera were used to measure Hcy levels by using commercial kits (Siemens Medical Solutions Diagnostics) in Immulite 2000 and to measure fasting blood glucose, total cholesterol (T-chol), triglyceride (TG), and high density lipoprotein cholesterol (HDL-chol) concentrations by using commercially available Abbott kits in autoanalyzer (Aeroset, U.S.A). Low-density lipoprotein cholesterol (LDL-chol) concentrations were calculated according to Friedewald's formula (Friedewald et al. 1972). Serum PON and AE activities were evaluated by the spectrophotometric methods described by Eckerson et al. (1983) and Haagen and Brock (1992), and were expressed in terms of "U/L" and "kU/L", respectively.

Statistical Analysis

Statistical analysis was performed using statistical software SPSS for Windows 13.0 (Chicago, IL), and all continuous variables were summarized in terms of means (± standard deviation). Approximate normal distribution was assessed by Shapiro-Wilk test. The differences between the groups were determined by Independent Sample T-test for variables with normal distribution or by Mann-Whitney U test for variables that are not normally distributed. Pearson correlation analysis was performed to test the relationship between Hcy

concentrations, MetS predictors, PON-1 and AE activities. A value of p <0.05 was considered statistically significant.

Results

Demographic data of subjects with schizophrenia and healthy controls were statistically comparable (Table 1). The frequency of ATP-III (AHA) metabolic syndrome criteria in the two groups are given in Table 2. Metabolic syndrome frequency was not different between controls (27.6 %) and study group (24.4 %). Serum lipid concentrations (T-chol, TG, HDL-chol, and LDL-chol) were not different in the two groups, either (Table 3). Mean PON activity was lower in subjects with schizophrenia (182± 82 U/L) compared to controls (216 ± 110 U/L); however, the difference was not statistically significant. The AE activities were not altered in the study group compared to controls. Disease duration was not different in study subjects with (16±8 years) or without (15±9 years) metabolic syndrome.

Table 1. Demographic characteristics of subjects with schizophrenia and controls.

	Subjects (n=45)	**Controls (n=43)**	**p**
Age (years)	39 ± 11	37 ± 9	0.379
Female n (%)	21 (47)	19 (44.2)	0.815
Male n (%)	24 (53)	24 (55.8)	0.815
Smoker n (%)	20 (44.4)	21 (48.8)	0.680
BMI	27.8 ±5.6	26.8 ± 4.2	0.293
SBP (mmHg)	114 ± 13	118 ± 10	0.081
DPB (mmHg)	74 ± 8	72 ± 7	0.109
Disease Duration (years)	16 ±9		

BMI: Body mass index; DPB: Diastolic blood pressure; SBP: Systolic blood pressure

Serum homocysteine concentrations of schizophrenia group were significantly higher than that of controls (p<0.05) (Table 3). When analyzed in terms of gender, Hcy levels in schizophrenia group were significantly higher in male subjects (18±9 μmol/L) compared to those in females (12±3 μmol/L) (p<0.001). There was not any significant difference in Hcy concentrations of male subjects (12±8 μmol/L) and female subjects (12±4 μmol/L) in the control population.

Table 2. The frequency of ATP-III (AHA) metabolic syndrome criteria in subjects with schizophrenia and controls

ATP-III (AHA) criteria	**Subjects (n=45)**	**Controls (n=43)**	**p**
Waist circumpherence n(%) (F>88 cm; M>102 cm)	23(51.1)	17 (39.53)	0.276
Blood pressure n(%) (Systolic/Diastolic) (≥130/85 mmHg)	7 (15.6)	5(11.6)	0.591
HDL-cholesterol n(%) (F<50 mg/dL; M<40 mg/dL)	26(57.8)	25(58.1)	0.972
Triglyceride n(%) (≥150 mg/dL)	13(28.9)	15(34.9)	0.546
Fasting blood glucose n(%) (≥100 mg/dL)	5(11.1)	2(4.7)	0.435
Number of (+) criteria			
0 n(%)	9(20)	13(30)	0.268
1 n(%)	13(28.9)	11(26)	0.728
2 n(%)	12(26.7)	7(16)	0.236
3 n(%)	8(17.8)	10(23)	0.524
4 n(%)	2(4.4)	1(2.3)	0.682
5 n(%)	1(2.2)	1(2.3)	0.986

F: Female; M: Male; HDL: High density lipoprotein

Table 3. Serum lipids, paraoxonase and arylesterase activities and homocysteine concentrations in subjects with schizophrena and controls.

	Subjects (n=45)	**Controls (n=43)**	**p**
Total cholesterol (mg/dL)	203 ± 59	194 ± 45	0.445
Triglyceride (mg/dL)	134 ± 70	131 ± 58	0.997
HDL-cholesterol (mg/dL)	45 ± 11	45 ± 9	0.732
LDL-cholesterol	123 ±35	121 ± 27	0.613
Paraoxonase (U/L)	182± 82	216 ± 110	0.277
Arylesterase (kU/L)	88 ± 31	88 ± 24	0.847
Homocysteine (μmol/L)	15 ± 8	12 ± 3	0.019

HDL: High density lipoprotein; LDL: Low density lipoprotein

Serum Hcy concentrations were not different between subjects with and without metabolic syndrome in patient (14±4 μmol/L and 16±9 μmol/L) and control (12±3 μmol/L and 13±7 μmol/L) groups, respectively (Table 4). Hcy levels of subjects in schizophrenia group were not correlated with any of the MetS predictors: waist circumference (r=0.064), BMI (r=-0.058), systolic blood pressure (r=0.0159), diastolic blood pressure (r=0.085), TG (r= 0.042), HDL-chol (r=-0.281) and fasting glucose (r=0.068). Serum Hcy concentrations were also not correlated with PON-1 and AE activities.

Atypical antipsychotic drugs used in the present study were classified into three groups according to their risk of causing metabolic syndrome (Nasrallah et al. 2004). Namely, Group 1 consisted of clozapine and olanzapine, Group 2 consisted of risperidone and quetiapine, and Group 3 consisted of ziprasidone, aripiprazole, and amisulpride. There was not any statistical difference in metabolic syndrome rates detected in the three groups (31%, 19%, and 17%, respectively).

Table 4. Paraoxonase, Arylesterase activities and Homocysteine levels in subjects with schizophrenia and controls with or without metabolic syndrome.

	Subjects (n=45)			**Controls (n=43)**		
	MetS (+) (n=11)	MetS (-) (n= 34)	p	MetS (+) (n= 12)	MetS (-) (n=31)	p
Paraoxonase (U/L)	185± 100	181± 76	0.866	215± 111	216± 113	0.724
Arylesterase (kU/L)	84 ± 34	89± 20	0.847	83 ± 27	88 ± 33	0.995
Homocystein (μmol/L)	14 ± 4	16 ± 9	0.948	12 ± 3	13 ± 7	0.481

MetS: Metabolic syndrome

Discussion

The main outcome of this study is significantly higher serum Hcy concentrations in schizophrenic subjects on AA treatment for at least three months. Previous results about serum Hcy levels in schizophrenia are quite discrepant. Contrary to our elevated Hcy results, Bicikova et al. (2011) reported that six months of AA treatment did not cause any significant change in Hcy levels in individuals with schizophrenia, and Wysokinski et al. (2013) pointed no significant difference between Hcy levels of subjects on chlorpromazine treatment and healthy controls. However, in the same study, Wysokinski et al. (2013) reported higher serum Hcy levels in male subjects compared to female subjects, parallel to our findings with higher Hcy levels in male subjects. Later, Misiak et al. (2014) reported elevated Hcy levels after 12 weeks of AA treatment and concluded that AA treatment might worsen metabolic profile by increasing Hcy levels and affecting one-carbon metabolism. Contrary to the deduction arrived by Misiak et al. (2014), we suggest that elevation of Hcy levels are not related to MetS in schizophrenia. In the present study, study population and control subjects were matched according to the predictors of MetS, and Hcy levels were higher in subjects with schizophrenia than in controls, independent of the presence of MetS. Also, comparable Hcy levels in study subjects and controls with or without MetS suggest that elevations in Hcy concentrations are not influenced by MetS (Table 4). In addition, the lack of a correlation between MetS predictors and Hcy levels in schizophrenia group brings to mind that elevated Hcy levels are not responsible for the development of metabolic syndrome per se.

Wysokinski et al. (2013) have suggested that higher Hcy levels in male subjects could be because of the greater lean body mass of the men. Larger muscle mass metabolizes a greater amount of Met to provide methyl group for the synthesis of creatine, eventually forming a more significant amount of Hcy. However, their observation applied to both schizophrenic subjects and healthy controls in their study. In the present study, higher Hcy levels in males were detected only in the study group. Therefore, attributing this elevation to the fat-free mass of male subjects would not be proper according to the results of the present study. As a matter of fact, significantly higher Hcy levels in all schizophrenic subjects compared to controls emphasizes the risk high Hcy levels may cause to schizophrenic individuals on AA treatment.

PON is known for its cardioprotective effects. Reduced PON activity is associated with an increased risk of CVD and MetS. Gilca et al. (2014) pointed to early studies which confirm that individuals with low PON-1 activity are at greater risk of cardiac pathologies. PON activity is studied in schizophrenia, and lower levels were indicated to be against cardiovascular health (Sarandol et al. 2005, Gilca et al. 2014). In line with the findings of Sarandol et al. (2005) and Gilca et al. (2014), lower, but statistically not significant, PON activities were detected in the schizophrenia group in the present study, while the enzyme activities were similar in schizophrenic individuals with and without MetS. AE activities were not different between study subjects and controls. This supports the idea that PON enzyme activity may be impaired by elevated Hcy levels in schizophrenia. Studies about the effects of AA on PON-1 activity indicate varying results. While Gilca et al. (2014) reported increased PON and AE

activities in clozapine and risperidone treated individuals, and Abdel-Salam et al. (2018) reported increased PON-1 activity in clozapine treated schizophrenic rat brains, Unsal et al. (2013) reported varying PON-1 activities in schizophrenic subjects taking different atypical antipsychotic medications. Gunes et al. (2016) found higher AE levels in subjects taking atypical antipsychotics while PON-1 activity was not changed compared to controls. In a recent review, Moreira et al. (2019) suggested that both PON and AE enzymes decreased in individuals with first-episode schizophrenia, which could be normalized with certain antipsychotic treatment. Later, in a more recent meta-analysis, Goh et al. (2022) suggested that PON-1 activity was not altered by antipsychotics, especially atypical antipsychotics. The above-mentioned reports of differing results show that an exact consensus has not been reached yet, therefore, new reports on PON and AE activities in schizophrenia would provide new aspects on this matter. Although not significant, lower PON activity observed in the present study suggests that the enzyme activity tends to be impaired in schizophrenia regardless of MetS.

The small number of subjects enrolled in this study is a limitation. A larger subject group would provide strength in statistical analysis. Also, with a more significant number of study population on treatment with different AA, it would be possible to statistically evaluate the influence of subgroups of AA on PON-1 and Hcy levels and their relation to MetS indicators. Data from the drug naïve period of the study population would uprate the study by providing means to discuss the influence of AA on the results. Further investigations with a larger drug naïve study population that will be treated with different AA would improve the discussion on the effects of AA on Hcy and PON-1 status and their relevance to MetS in schizophrenia patients.

Conclusion

The results of this study indicate that schizophrenic individuals on AA treatment have increased levels of Hcy compared to healthy controls and this is not influenced by the presence of MetS. We suggest that AA treatment is accompanied with high Hcy levels which may further threatencardiovascular health by impairing PON activity. Future studies with schizophrenic subjects on different AA treatments would provide new insights to the effects of different groups of AA on Hcy metabolism and PON-1 activity. Results of these studies may guide the selection of the AA to be preferred in subjects with schizophrenia.

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