



# Correlation between serum concentrations of homocysteine, folate and vitamin B12 in patients with schizophrenia

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## ABSTRACT

**Introduction:** The role of hyperhomocysteinemia in psychotic disorder can be explained by partial antagonism of homocysteine on NMDA-glycine receptor. Plasma concentration of homocysteine is an indicator of the status of the B-vitamins (folate, B12, B6). Folate deficiency may have different effects on the neurochemical processes of schizophrenia. This suggests that the association between elevated levels of homocysteine and schizophrenia is biologically very likely.

**Methods:** The study was consisted of 20 patients with schizophrenia and 20 healthy controls. We investigated the levels of serum homocysteine concentration using AxSYM (Abbott), levels of folate assay is two-step immunoassay to determine the presence folate in human serum using CMIA (chemiluminescent microparticle immunoassay) technology and AxSYM Holo Tc is microparticle enzyme immunoassay (MEIA) for the quantitative determination of human holo TC in serum and determination deficit of vitamin B 12.

**Results:** The patients group has higher levels of homocysteine in compare with controls group for 3.85  $\mu\text{mol/L}$  while the concentration of folate in the group of patients was lower for 9.17  $\text{ng/mL}$ . The mean level of vitamin B-12 in investigation groups were in reference range 19.1-119  $\text{pmol/L}$ , but patient group have lower average concentration of vitamin B-12 lower for 24.81  $\text{pmol/L}$  compared to the control group.

**Conclusion:** Our results showed that homocysteine concentration is inversely proportionate to folate concentration, i.e. as homocysteine concentration in serum increases, folate concentration falls. Schizophrenic patients with elevated tHcy level and low folate levels should have vitamin supplementation with folic acid.

**Keywords:** Schizophrenia, homocysteine, folate, vitamin B-12.

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## INTRODUCTION

Conceptualization of glutaminergic system in the last fifty years follows the historical development of models phencyclidine (PCP) in patients who suffering from schizophrenia, a description of its



psychomimetic effect, through the discovery of N-methyl-D-aspartate glutamate receptor (NMDAR), and finally the nineties years set new treatment strategies to base on these receptors (1, 2). NMDAR antagonists induce an increase of the positive and negative symptoms of schizophrenia. In this connection we now have several hypotheses that explain the mechanism by which NMDAR dysfunction leads to abnormalities in thinking, perception disorders, bizarre behavior and cognitive damage, which schizophrenia remains of intrigue when it comes to the status of reality as the notion of mental deterioration, as well as several theories in the new concept of treatment. Oxidation of homocysteine leads to the formation homocysteine sulfuric acid and homocysteine acid; both products have expressed excitotoxic action of the different subtypes of the N-methyl-D-aspartate (NMDA) glutamate receptor. Excitotoxic cell type was observed when human cells in different parts of the brain exposed to homocysteine excitotoxic acids and amino acids. Recent studies in rats have shown that homocysteine causes DNA damage to neurons inducing apoptosis of hypersensitivity to excitotoxicity. In the brain, there is a limited capacity for homocysteine metabolism. In addition, folate metabolism play a critical roles in the metabolism of homocysteine (4). The level of 5-methyltetrahydrofolate in cerebrospinal fluid is at least three times that found in plasma and an active transport process exists at the blood-brain-barrier. The folates have important role in the brain and the necessity for protection against the effects of deficiency (5). Tests on rats have shown that elevated homocysteine leads to apoptosis of neurons in the hippocampus. Relatively large storage of folate in CSF provides the brain with folate and thereby protects nerve cells from the toxic effects of increased concentrations of homocysteine. Besides folate deficiency may have different effects on the neurochemical processes of schizophrenia, because it works as a carbon donor in the synthesis of glycine from serine. Folate is also involved in the synthesis of dopamine, norepinephrine and serotonin through pathways the methylation of S-adenosyl-methionine and conversion of methionine to homocysteine (6). Homocysteine is an amino acid produced by demethylation of methionine, an essential amino acid that in the body intake of food. Homocysteine was first described in 1932 in the works by Butz and Vigneauda that homocysteine synthesis activity concentrated strong

acid on methionine. In the body comes from food or produced during degradation of endogenous proteins. Methyl group of methionine is activated by switching to S-adenosyl-methionine (SAM). The reaction catalyzes of L-methionine-S-adenosyltransferase the presence of ATP. After the transfer of the methyl group exceeds S-adenosyl-methionine in thioester S-adenosyl-homocysteine (SAH). S-adenosyl-methionine is a donor of numerous reactions in the brain, including many that are involved in the synthesis and metabolism of monoamines such as dopamine, norepinephrine and serotonin (6). This suggests that the association between elevated levels of homocysteine and schizophrenia is biologically very likely. Numerous epidemiological studies have linked increased levels of homocysteine with vascular disease, dementia, defects of fetal development, increasing the level of mortality and with neuropsychiatric disorders (2) such as schizophrenia, bipolar affective disorder and depression (6,7,8). Homocysteine is at about 45% of elderly patients increased and its concentration correlates well with the severity of the memory functions. Therefore homocysteine it is better for diagnosis of cognition (cognitive impairment) than the concentration of folate and vitamin B12 in serum (9).

Today there is interest in measuring the biologically active form of cobalamin. The vitamin B 12 (cobalamin) in serum is bound to two proteins, transcobalamin (TC) and haptocorrin (HC). About 20% of cobalamin is related to transcobalamin and it is biologically active, while 80% is related to haptocorrin is biologically inactive. The transcobalamin-vitamin B-12 complex is called holotranscobalamin (Holo Tc) and it is used in vitro diagnostic assay for the quantitative determination of cobalamin. The reduced concentration of Holo Tc, it is an indicator of deficit vitamin B 12. Notably, low values have been reported in vegetarians and populations with low intake of vitamin B 12. The tests for measuring total vitamin B 12 are based on the measurement of active and inactive fractions, but very often do not correlate with existing symptoms of the deficit. The reference area of vitamin B 12 is difficult to determine because it is too close to «normal» samples. Holo Tc levels reflect vitamin B 12 status, independent of recent absorption of the vitamin (10,11).

Homocysteinaemia is a newly defined term connected to the increased risk of atherothrombotic

and atherosclerotic systemic and retinal vascular occlusive diseases, and its role in the course of many anatomical or functional abnormalities of the vessels of the optic nerve head such as arteriosclerosis or vascular dysregulation, homocystein might be the causative factor (12,13). Some studies showed that elevated Hcy may increase the risk of retinal vascular diseases, such as retinal artery and vein occlusion and non-arteritic ischemic optic neuropathy (14, 15). Hcy-induced vascular problem may be a multifactorial case, including direct toxic damage to the endothelium, stimulation of proliferation of smooth muscle cells, enhanced low density lipoprotein peroxidation, increased platelet aggregation, and effects upon the coagulation system (16).

Maybe, this reason of much work in the cognitive neuroscience of schizophrenia has focused on attention, memory, and executive functioning. To date, less work has focused on perceptual processing. However, perceptual functions are frequently disrupted in schizophrenia, and thus this domain has been included available ophthalmology tests in this article, how we can describe the basic science presentation and the breakout group discussion on the topic of perception when we use some test for the assessment of cognitive function in schizophrenia. The importance of perceptual dysfunction in schizophrenia, the nature of perceptual abnormalities in this disorder, and the critical need to develop perceptual ophthalmology tests appropriate for future clinical trials and validity of some tests for the assessment of cognitive function in schizophrenia were discussed.

## METHODS

### Patients

The patients group consisted of inpatients (n=20) with Schizophrenia (Sch) diagnosed according to the tenth revision of the International Classification of Diseases (ICD-10), treated at the Psychiatric Clinic, Clinical Centre University of Sarajevo (CCUS). The patients were followed for eight weeks during 2012. All participants signed an informed consent and study was approved by the Ethics Committee of the Clinical Center of the University of Sarajevo. The study was, for the most part, conducted via the prospective method of clinical research and partly as

a descriptively controlled study. The patients were treated with typical antipsychotics (haloperidol and fluphenazine) (n = 14) and atypical antipsychotics (olanzapine and risperidone) (n = 6) for at least eight weeks.

The inclusion criteria were female and male patients with a diagnosis of schizophrenia according to ICD-10 criteria (International Classification of Diseases); The presence of positive and negative symptoms, cognitive deficits and functioning on a social level; Antipsychotic therapy, typical or atypical; Subjects 18-65 years of age; One or more hospitalizations. The exclusion criteria were comorbidity; organic brain damage; other medical conditions (diabetes mellitus, hypertension, neurological disorders, inflammatory disease or gastroenterological disease); alcohol and drug abuse.

### Blood samples

The patient samples of blood were collected in serum separation Vacutainer test tubes (Beckton Dickinson, Rutherford, NJ 07,070 U.S.) in volume of 3.5 mL. Test tubes with gel were used. After collection, samples were placed in ice and after 30 to 60 minutes, samples were obtained by centrifugation at 3000 rpm using centrifuge (Sigma 4-10). After centrifuging, serum concentration of homocysteine, folate, active form of vitamin B-12 and creatinine were determined.

### Determination of homocysteine (Hcy)

The value of serum homocysteine concentration was determined using AxSYM (Abbott), based on measurements of fluorescence polarization immunoassay (FPIA) technology. The reaction principle is conversion of homocystine, mixed disulfide and protein-bound forms of homocysteine in the sample to form of free homocysteine by the use of dithiothreitol (DTT). After that free homocysteine is converted to S-adenosyl-L-homocysteine (SAH). Under physiological conditions, SAH - hydrolases converts SAH to homocysteine. Existing methods is to determine L-homocysteine in human serum. Normal concentration of homocysteine in serum of women is 3.36-20.44  $\mu\text{mol/L}$  and in men is 5.90-16  $\mu\text{mol/L}$  (17). The creatinin was determined using automatic analyzer Dimension (Dade Behring). Method for determination of creatinine is a modification of the kinetic reaction of Jaffee. The reference value for

serum creatinine concentration is 45-115  $\mu\text{mol/L}$  (18).

### Determination of folate

All immunoassays require the use of labeled material in order to measure the amount of antigen or antibody. A label is a molecule that will react as a part of the assay, so a change in signal can be measured in the blood after added reagent solution. CMIA (chemiluminescent microparticle immunoassay) is non-competitive sandwich assay technology to measure analytes. The amount of signal is directly proportional to the amount of analyte present in the sample. Architect folate assay is two-step immunoassay to determine the presence folate in human serum using CMIA technology. Two pre-treatment steps mediate the release of folate from endogenous folate binding protein. In pre-treatment step 1 sample and pre-treatment reagent 2 (dithiothreitol or DDT) are aspirated and dispensed into a reaction vessels (RV). In pre-treatment step 2, an aliquot of sample/pre-treatment reagent 2 mixture is aspirated and dispensed into a second RV. Pre-treatment reagent (KOH) is then added. An aliquot of the pre-treated sample is transferred into a third RV, followed by the addition of folate binding protein (FBP) coated paramagnetic microparticles and assay specific diluent. Folate presented in the sample binds to the FBP coated microparticles. After washing, pterotic acid-acridinium labeled conjugate is added and binds to unoccupied sites on the FBP-coated microparticles. Following another incubation and wash, pre-trigger and trigger solutions are then added to the reaction mixture. The pre-trigger solution (hydrogen peroxide) creates an acidic environment to prevent early release of energy (light emission), helps to keep microparticles from clumping and splits acridinium dye off the conjugate bound to the microparticle complex (this action prepares the acridinium dye for the next step). The trigger solution (sodium hydroxide) dispenses to the reaction mixture. The acridinium undergoes an oxidative reaction when is exposed to peroxide and an alkaline solution. This reaction causes the occurrence of chemiluminescent reaction. N-methylacridone forms and releases energy (light emission) as it returns to its ground state. The resulting chemiluminescent reaction is measured as relative light units (RLU). A direct relationship exists between the amount of folate in the sample and

RLU detected by Architect System optics. The reference value for serum folate concentration is 7.0-31.4 ng/mL (19).

### Determination of active B-12

AxSYM Holo Tc is microparticle enzyme immunoassay (MEIA) for the quantitative determination of human holo TC in serum and determination deficit of vitamin B 12. Microparticles are coated with an Anti-Holo Tc monoclonal antibodies in the presence of human antigens on the Holo Tc microparticles arises immune complex. On Anti-Holo Tc antibodies present a conjugate of alkaline phosphatase in the next reaction, which reacts with the substrate 4-methylumbelliferyl phosphate (MUP). The resulting fluorescent product is measured by MEIA optical system. The reference value for the healthy population Holo Tc is 19.1-119 pmol/L (20).

### Statistical analysis

The results were statistically analysed using SPSS version 12 and Microsoft Office Excel 2003. Average values, standard deviation (SD) and Pearson correlation coefficient ( $r$ ) were calculated, as well Wilcoxon signed rank test with statistical significance level of 0.05  $P < 0.05$ .

## RESULTS

The investigation included 20 patients with schizophrenia and 20 healthy subjects. The study included 6 (30%) men and 14 (70%) women in control group. The group with schizophrenia have 5 (25%) men and 15 (75%) women. The average age in the control group was 49.45 years and in schizophrenia patients was 44.5 years. Normal homocysteine concentration in serum is 3.36-20.44  $\mu\text{mol/L}$  for women and 5.90-16  $\mu\text{mol/L}$  for men. The reference folate concentration is 7.0-31.4 ng/mL and vitamin B-12 19.1-119 pmol/L.

The mean concentration of homocysteine, folate and vitamin B-12 in schizophrenia patients and control group are shown in Table 1. The patients with schizophrenia have higher levels of homocysteine in compare with controls group for 3.85  $\mu\text{mol/L}$  while the concentration of folate in the group of patients was lower for 9.17 ng/mL. The patients with schizophrenia have a folate deficiency. The mean level of vitamin B-12 in investigation groups were in ref-

TABLE 1. The mean concentration of homocysteine, folate and vitamin B-12 in schizophrenia patients and control group.

Groups		Homocysteine ( $\mu\text{mol/L}$ )	Folate ( $\text{ng/mL}$ )	Vitamin B-12 ( $\text{pmol/L}$ )
Schizophrenia patients (N=20)	$X_{\text{sr}}$	14.22	5.94	54.00
	S.D.	4.19	2.30	23.65
	S.E.	0.93	0.51	5.28
Control group (N=20)	$X_{\text{sr}}$	10.37	15.11	78.81
	S.D.	2.16	7.00	24.25
	S.E.	0.48	1.56	5.42

TABLE 2. Comparison of serum concentration of homocysteine, folate and vitamin B-12 in schizophrenia patients and control group.

	Homocysteine	Folate	Vitamin B-12
Z	-2.800	-3.920	-2.800
P	0.005*	0.000*	0.005*

\*  $P < 0.05$  (Wilcoxon signed ranks)

TABLE 3. Correlation between homocysteine and vitamins in patients with schizophrenia.

		Folate	Vitamin B-12
Schizophrenia patients	r	-0,52	-0,47
	p	0,017*	0,035*

\* Statistical significant for  $P < 0.05$

erence range 19.1-119  $\text{pmol/L}$ , but patient group have lower average concentration of vitamin B-12 lower for 24.81  $\text{pmol/L}$  compared to the control group. Folate deficiency significantly changes the concentration of homocysteine, which could affect the differences between patients with schizophrenia and control group.

It is indicated that high level of homocysteine follows low level of folate in serum at patients with schizophrenia.

We have shown in Table 2. Z and P values mean serum homocysteine, folate and vitamin B-12 concentration in patients and control subjects. Using Wilcoxon signed ranks test we have concluded that average concentration of homocysteine in schizophrenia patients were significantly different ( $P < 0.05$ ) from serum concentration in control subjects. There was a significant difference in folate serum concentration between patient group and control group for  $P < 0.05$ . According Wilcoxon signed ranks test

mean vitamin B-12 concentration was significant for  $P < 0.05$  in investigated groups.

The correlation between homocysteine and vitamin levels in patients serum are shown in Table 3. There was a significant difference between the mean serum homocysteine and folate ( $P < 0.05$ ) with a negative Pearson correlation coefficient ( $r = -0.52$ ) in the group of patients. Using the same test, a significant difference between the mean serum homocysteine and vitamin B-12 ( $p < 0.05$ ) with a negative Pearson correlation coefficient ( $r = -0.47$ ).

## DISCUSSION

The role of hyperhomocysteinemia in psychotic disorder can be explained by partial antagonism of homocysteine on NMDA-glycine receptor (21). Epidemiological studies show a correlation between total plasma homocysteine concentration and the risk of neurodegenerative diseases (22). Plasma concentration of homocysteine is an indicator of the status of the B-vitamins (folate, B12, B6). It was found that the values of homocysteine levels are significantly elevated in young male patients with schizophrenia and BP, especially those who show signs of cognitive deterioration, compared to the general population (23). However, there are studies whose results indicate no difference in homocysteine levels between bipolar patients and healthy controls (24). Increased levels of homocysteine can cause apoptosis and exocytosis as important mechanisms of neurodegeneration. The brain tissues utilize three mechanisms for maintaining low steady state concentrations of homocysteine: 1) efficient recycling through cobalamin-dependent methionine synthase, given an adequate supply of cobalamin and folate; 2) catabolism through CBS to cystathionine; 3) export homocysteine into the circulation (25). In our study group patients with schizophrenia have higher levels of homocysteine in compare with controls group for 3.85  $\mu\text{mol/L}$  while the concentration of folate in the group of patients was lower for 9.17  $\text{ng/mL}$ . Our results are compared with the results Mabrouk et al (26) have shown that the increased value of homocysteine and a lower value of folate in patients with schizophrenia compared with the control group. The low folate status in schizophrenics and folate-responsive schizophrenic-like behavior are connected with deficiency of MTHFR of TT genotype (27). Eren et al (28) have shown to the increased value of

homocysteine in patients group with schizophrenia than in the control group, but no significant differences in the values of folate and vitamin B12, which is possible due to prolonged use of typical neuroleptics. These results are not consistent with our results because we also had a larger number of patients who were treated with typical neuroleptics. In our study presented Z and P values mean serum homocysteine, folate and vitamin B-12 concentration in patients and control subjects. Using Wilcoxon signed ranks test we have concluded that average concentration of homocysteine in schizophrenia patients were significantly different ( $P < 0.05$ ) from serum concentration in control subjects. The reason for this is the course of the illness, because in the work of Erna et al it was a chronic schizophrenic patient. Low folate/high homocysteine level leads to increased sensitivity of neurons and brain damage. We get the following results, there was a significant difference between the mean serum homocysteine and folate ( $P < 0.05$ ) with a negative Pearson correlation coefficient ( $r = -0.52$ ) in the group of patients. Using the same test, a significant difference between the mean serum homocysteine and vitamin B-12 ( $p < 0.05$ ) with a negative Pearson correlation coefficient ( $r = -0.47$ ). We have got a good correlation of homocysteine with folate and vitamin B-12. The negative Pearson correlation coefficient we could explain that high level of homocysteine is probably resulted with low folate serum concentration. In our study we have got vitamin B-12 in reference range which could be explained with wide range of vitamin B-12 in human body. Epidemiological studies have found a link between folate deficiency and hyperhomocysteinemia in neurodegenerative and neuropsychiatric disorders, including Alzheimer's and Parkinson M., depression and schizophrenia. There is also evidence on the connection between B-vitamin deficiency and depression (29). Folic acid and SAM can be used as a complementary means for the treatment of depression. On the other hand, folate deficiency in depressed patients may be a consequence of inadequate nutrition. Regardless of whether folate deficiency in primary or secondary depression, administration of folate may be useful in recovering from depression and improve mental status. It would be interesting to extend our research to other psychiatric diagnostic groups such as depression and bipolar affective disorder.

It is known that a diet rich in animal protein may in-

crease, and foods rich in beans and green vegetables to lower homocysteine levels. Different groups of drugs, such as drugs for lowering fat (fibrates and niacin), oral hypoglycemics (metformin), insulin, drugs used to treat rheumatoid arthritis and anti-convulsants may cause an increase in serum levels of homocysteine (30), which could in the future be interesting in expanding the study introduce more detailed and complete test diet. With regard to gender differences in the prevalence of hyperhomocysteinemia results of numerous studies indicate that the values of homocysteine levels are generally higher in men (31). All of the above would be fully subject of our next study, given that they are now working on the preliminary results.

## CONCLUSION

These findings support the hypothesis that altered levels of homocysteine, folate and vitamin B12 may coexist in patients with schizophrenia and contribute to pathophysiological aspects of this illness. The homocysteine could be an independent risk factor for neuropsychiatric disorders and risk factor for development of cerebrovascular disease. In our group of schizophrenia patients we have a limited number of patients and we have not informations about concentration of homocysteine, folate and vitamin B-12 during schizophrenia treatment. The hyperhomocysteinemia is presented in about 25 % and low folate levels in 60 % of schizophrenia patients. In patients group homocysteine level were elevated compared to the levels of controls when folate levels were low, these results indicate that enzymatic defect could be involved. Our results showed that homocysteine concentration is inversely proportionate to folate concentration, i.e. as homocysteine concentration in serum increases, folate concentration falls. The schizophrenia patients with elevated tHcy level and low folate levels should have vitamin supplementation with folic acid. This would be the view of the preliminary results of our research, which in the future demanded a larger sample, the relationship between these biochemical parameters related to the predominance of positive or negative symptoms of schizophrenia, with the inclusion of other diagnostic entities, depression and bipolar affective disorder, and complete processing of data related to the metabolic syndrome and nutrition, which will be planned.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**REFERENCES**

- Coyle JT. The NMDA receptor and schizophrenia: a brief history. *Schizophr Bull.* 2012. In press.
- Javitt DC. Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. *Schizophr Bull.* In press.
- Bolander-Gouaille C, Bottiglieri T. Homocysteine related vitamins and neuropsychiatric disorders, Springer-Verlag. France, 2007:15-57,109-163.
- Broch O, Ueland P.M. Regional distribution of homocysteine in the mammalian brain. *J. Neurochem.* 1984;43:1755-1757.
- Herbert V, Zalusky R. Selective concentration of folic acid activity in cerebrospinal fluid. *Fed. Proc.* 1961;20: 453.
- Bottiglieri T, Laundry M, Crellin R, Toone BK, Carney MWP, Reynolds EH. Homocysteine, folate, methylation, and monoamine metabolism in depression. *Journal of Neurology Neurosurgery and Psychiatry.* 2000;69(2):228–232.
- Muntjewerff JW, Kahn RS, Blom HJ, den Heijer M. Homocysteine, methylenetetrahydrofolate reductase and risk of schizophrenia: a meta-analysis. *Mol Psychiatry.* 2006;11(2):143-9.
- Kevere L, Purvina S, Bauze D, Zeibarts M, Andrezina R, Rizevs A, Jelisejevs S, Piekuse L, Kreile M, Purvins I. Elevated serum levels of homocysteine as an early prognostic factor of psychiatric disorders in children and adolescents. *Schizophr Res Treatment.* 2012.
- Kang S.S, Wong P.W.K. Genetic and nongenetic factors for moderate hyperhomocysteinemia. *Atherosclerosis.* 1996;119:135-138.
- Lothar T. Labor und Diagnose. TH-Books Verlagsgesellschaft mbH, Frankfurt/Main, 5. erweiterte Auflage. 2000;1507-1513.
- Kajan J.P, Twardowski T, Jakubowski H. Mechanisms of homocysteine toxicity in humans. *Amino. Acids.* 2007;32: 561-572.
- Flammer J, Orgul S, Costa VP, Orzalesi N, Kriegelstein GK, Serra LM, Renard JP, Stefansson E: The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res.* 2002;21:359-393.
- Hayreh SS: Blood flow in the optic nerve head and factors that may influence it. *Prog Retin Eye Res.* 2001;20:595-624.
- Bousse V, Newman NJ, Sternberg P: Retinal vein occlusion and transient monocular visual loss associated with hiperhomocysteinemia. *Am J Ophthalmol.* 1997;124:257-260.
- Brown BA, Marx JL, Ward TP, Hollifield RD, Dick JS, Brozetti JJ, Howard RS, Thach AB: Homocysteine: a risk factor for retinal venous occlusive disease. *Ophthalmology.* 2002;109:287-290.
- Finkelstein JD: The metabolism of homocysteine: pathways and regulation. *Eur J Pediatr.* 1998;157:40-44.
- Operator Manual AxSym System. Abbott Diagnostic Homocysteine, REF 5F51 ABBL 143/R09, 2012.
- Operator Manual Dimension System. Dade Behring 2000, pp. 51-60.
- Operator Manual ARCHITECT I 2000 SR Abbott Diagnostic Folate, REF 1P74, 34-5955/R03, B1P740, 2010.
- Operator Manuel AxSym System. Abbott Diagnostic Active B-12, REF 1P43-20 ABOL039/R1, 2007.
- Neeman G, Blanaru M, Bloch B, Kremer I, Ermilov M, Javitt DC, Heresco-Levy U. Relation of plasma glycine, serine, and homocysteine levels to schizophrenia symptoms and medication type. *Am J Psychiatry.* 2005;162(9):1738-40.
- Stanger O, Fowler B, Piertzik K, Huemer M, Haschke-Becher E, Semmler A, Lorenzl S, Linnebank M. Homocysteine, folate and vitamin B12 in neuropsychiatric diseases: review and treatment recommendations. *Expert Rev Neurother.* 2009;9(9):1393-412.
- Osher Y, Sela BA, Levine J, Belmaker RH. Elevated homocysteine levels in euthymic bipolar disorder patients showing functional deterioration. *Bipolar Disord.* 2004;6(1):82-6.
- Bromberg A, Bersudsky Y, Levine J, Agam G. Global leukocyte DNA methylation is not altered in euthymic bipolar patients. *J Affect Disord.* 2009;118(1-3):234-9.
- Scott J.M, Molloy A.M, Kennedy D.G, Kennedy S, Weir D.G. Effects of disruption of trans methylation in the central nervous system: An animal model. *Acta. Neurol. Scand.* 1994;89 (154): 27-31.
- Mabrouk H, Douki W, Mechri A, Younes MK, Omezzine A, Bouslama A, Gaha L, Najjar MF. Hyperhomocysteinemia and schizophrenia: case control study. *Encephale.* 2011;37(4):308-13.
- Freeman JM, Finkelstein JD, Mudd, SH. Folate-responsive homocystinuria and „schizophrenia“. A defect in methylation due to deficient 5,10-methylenetetrahydrofolate reductase activity. *N Engl J Med* 1975;292:491-496.
- Eren E, Yeğin A, Yilmaz N, Herken H. Serum total homocystein, folate and vitamin B12 levels and their correlation with antipsychotic drug doses in adult male patients with chronic schizophrenia. *Clin Lab.* 2010;56(11-12):513-8.
- Obeid R, McCaddon A, Herrmann W. The role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric diseases. *Clin Chem Lab Med.* 2007;45(12):1590-606.
- Dierkes J, Westphal S. Effect of drugs on homocysteine concentrations. *Semin Vasc Med.* 2005;5(2):124-39.
- Applebaum J, Shimon H, Sela BA, Belmaker RH, Levine J. Homocysteine levels in newly admitted schizophrenic patients. *J Psychiatr Res.* 2004;38(4):413-6.