

Original Article

Red cell distribution width, mean platelet volume, and vitamin B₁₂ levels in patients with schizophrenia: an observational study

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Abstract: Objectives: Increasing evidence suggests an association between inflammation and schizophrenia. The aim of this study was to evaluate vitamin B₁₂, mean platelet volume (MPV) and red cell distribution width (RDW) levels in patients with schizophrenia. Materials and methods: Fifty-six patients diagnosed with schizophrenia and 30 age- and sex-matched controls were included in the study. Serum B₁₂, MPV and RDW levels were measured in all patients. Results: RDW levels were significantly higher in patients with schizophrenia than in the controls (P<0.001). MPV levels were increased in patients with schizophrenia; however, this increase was not statistically significant (P>0.05). Serum B₁₂ levels were significantly lower in patients with schizophrenia than controls (P<0.001). Conclusions: Our results demonstrated that schizophrenic patients had high RDW and MPV levels along with decreased B₁₂ levels. Increased inflammation may play a pathophysiological role in the development of atherosclerosis in schizophrenic patients.

Keywords: Schizophrenia, mean platelet volume, red cell distribution width, platelet number, vitamin B₁₂, atherosclerosis

Introduction

Schizophrenia is a chronic and severe psychiatric disease that affects approximately 1% of the population and causes disability [1]. Schizophrenia is a complex and multifactorial disorder with well-defined symptoms and a lifelong course. Evidence suggests that immunological and inflammatory mechanisms may play important roles in the pathophysiology of schizophrenia [2]. Previous studies have demonstrated an association between elevated plasma inflammatory biomarkers and increased risk of schizophrenia [3, 4]. Increasing evidence suggests that inflammatory mechanisms play important roles in the pathophysiology of schizophrenia. Various immune alterations, such as abnormal levels of inflammatory cytokines [5, 6] and pathogenic autoantibodies [7], have been observed in patients with

schizophrenia. Additionally, cardiovascular diseases occur more frequently in schizophrenic patients compared with the general population [8, 9]. Although several risk factors have been identified for the association between schizophrenia and cardiovascular diseases, the exact mechanisms remain unclear.

Platelets play an important role in thrombus formation and atherogenesis, a target for numerous anti-platelet agents developed over the years for the effective treatment of cardiovascular and cerebrovascular disease. Larger platelets are more active and contain more granules, which may lead to increased secretion of prothrombotic factors [10, 11]. Mean platelet volume (MPV) has been widely used as a marker of platelet function and reactivity. Recently, studies have reported increased MPV levels in patients with schizophrenia [12, 13].

The red cell distribution width (RDW), a measure of heterogeneity in the size of circulating red blood cells, is a component of the standard complete blood count (CBC). RDW is commonly used to discriminate between microcytic anemias due to iron deficiency and those due to thalassemia or hemoglobinopathies. Increased RDW levels are related to impaired erythropoiesis and erythrocyte degradation [14]. Increased RDW levels are associated with morbidity and mortality in chronic cardiac disease [15]; moreover, increasing evidence indicates that inflammation has a substantial role in pathogenesis. RDW is associated with inflammatory markers in numerous diseases [16]. To our knowledge, the association between RDW levels and schizophrenia has not been investigated.

Results from previous studies investigating vitamin B₁₂ levels in schizophrenic patients have been controversial. While some authors reported increased or decreased vitamin B₁₂ levels [17-19], others reported no significant change in vitamin B₁₂ levels in patients with schizophrenia [20]. Numerous studies have suggested an association between increased homocysteine levels and schizophrenia [21, 22], although there are also several contradictory studies [23, 24].

Increasing evidence indicates that inflammation is associated with schizophrenia. We hypothesized that high MPV and RDW levels might be associated with low vitamin B₁₂ levels in patients with schizophrenia. Therefore, we aimed to evaluate vitamin B₁₂, MPV and RDW levels in patients with schizophrenia.

Materials and methods

Subjects

This observational study included 56 patients with schizophrenia (29 females, 27 males; mean age, 34±10 years) from the Psychiatry Department at Harran University. Chronic schizophrenia was diagnosed by the consensus of two experienced psychiatrists according to the DSM-V criteria [25].

Patients with hypertension, liver or kidney diseases, coronary artery or heart valve diseases, neurologic deficits, pulmonary diseases or endocrine disorders during the study period were excluded from the study.

Thirty healthy subjects were enrolled in this study as a control group. Control subjects were asymptomatic with unremarkable medical histories and normal physical examinations. None of the control subjects took any medication or antioxidant vitamin supplementation, such as vitamins E and C.

The study was performed in accordance with the Declaration of Helsinki as revised in 2000. All subjects were informed about the study protocol, and written informed consent was obtained from each participant.

Mean platelet volume and red cell distribution width analyses

Complete blood counts, including platelet count, RDW and MPV levels, were obtained using an automatic blood counter (Beckman-Coulter, LH 780, USA).

Serum vitamin B₁₂ levels

Serum vitamin B₁₂ levels were measured using an automated chemiluminescence analyzer (Roche Diagnostics, Elecsys E170, Germany).

Statistical analysis

Results are presented as the means ± standard deviations. Student's t-test was used to compare variables of study subjects. Qualitative variables were assessed using the chi-square test. The results were considered statistically significant at *p* values below 0.05. Statistical analyses were conducted using SPSS® (version 20.0) for Windows.

Results

Clinical and demographic data of the study population are shown in **Table 1**. The mean age of schizophrenic patients was 34±10 years, and the mean age for control participants was 33±10 years. There were no statistically significant differences between the two groups with regard to age or gender (*P*>0.05) (**Table 1**).

Of the 56 schizophrenic patients, 27 (48.2%) were male, and 29 (51.8%) were female (32.5%). Of the 30 control subjects, 13 (43.3%) were male, and 17 (56.7%) were female (**Table 1**).

Platelet counts and RDW levels were significantly higher in patients with schizophrenia

B₁₂ & inflammation in schizophrenia

Table 1. Demographic and clinical parameters and serum vitamin B₁₂ and inflammation marker levels of patients with schizophrenia and control subjects

Parameters	Schizophrenia (n=56)	Controls (n=30)	P
Age (years)	34±10	33±10	0.630
Sex (female/male)	29/27	17/13	0.665
B ₁₂ (pg/mL)	204.79±55.89	256.57±77.49	0.001
RDW (%)	13.20±2.14	11.62±0.90	0.001
MPV (fl)	7.17±1.17	6.90±0.69	0.255
Platelet number (/mm ³)	262.54±66.31	306.72±79.86	0.008

Values are mean ± SD; Bold values indicate statistical significance; MPV: Mean platelet volume; RDW: Red cell distribution width.

Table 2. Vitamin B₁₂, mean platelet volume, red cell distribution width and platelet count in patients with schizophrenia according to gender

Parameters	Female (n=29)	Male (n=27)	P
B ₁₂ (pg/mL)	204.79±55.89	256.57±77.49	0.698
Platelet number (10 ³ /mm ³)	280.76±52.34	242.97±74.71	0.032
MPV (fL)	7.10±1.01	7.24±1.33	0.676
RDW (%)	13.42±2.28	12.96±1.99	0.430

Values are mean ± SD; Bold values indicate statistical significance; MPV: Mean platelet volume; RDW: Red cell distribution width.

than in the control group (P=0.008 and P<0.001, respectively). Although not statistically significant, MPV levels were increased in patients with schizophrenia (P>0.05) (**Table 1**).

Serum B₁₂ levels were significantly lower among patients with schizophrenia compared with controls (P<0.001) (**Table 1**).

When patients with schizophrenia were divided into two sub-groups according to gender, platelet numbers were significantly higher in females than in males (P=0.032). However, there were no statistically significant differences in terms of B₁₂, MPV and RDW levels (P>0.05) (**Table 2**).

Discussion

This is the first study demonstrating that schizophrenic patients have significantly higher RDW levels than control subjects. In addition, MPV levels were higher in patients with schizophrenia than controls; however, this difference was not statistically significant. Moreover, our results suggest that patients with chronic schizophrenia have lower serum B₁₂

levels compared with controls. Therefore, we hypothesized that high MPV and RDW levels may be associated with low vitamin B₁₂ levels in patients with schizophrenia.

Psychiatric diseases can be considered as stemming from inflammatory disorders, although the exact underlying mechanisms are not known. An increase in the inflammatory response may lead to inflammation, which in turn can stimulate microglia in the brain [26]. Several studies have investigated pro-inflammatory changes in schizophrenia [27, 28]. Some studies investigating pro-inflammatory cytokines in schizophrenic patients have reported increased TNFα and IL-6 levels associated with this disorder; pro-inflammatory cytokines and their receptors may represent therapeutic targets for treatment of schizophrenia [29, 30].

Patients with schizophrenia have shorter life spans than the general population [31, 32] and are associated with higher risk of respiratory, infectious and cardiovascular diseases [33]. These patients are reported to be at higher risk for cardiovascular diseases, and this risk is shown to be associated with characteristics of metabolic syndrome and dyslipidemia [34, 35]. There is a high prevalence of metabolic syndrome in these patients due to antipsychotic medication [36, 37]. Extensive evidence suggests that the prevalence of lipid and glucose metabolism disturbances is significantly higher in first-episode and drug-naive patients with schizophrenia than controls [38, 39]. Mortality rates due to obesity-related conditions, such as coronary heart disease, are high among those with schizophrenia [40].

Vitamin B₁₂ plays a very important role in the formation of red blood cells and maintenance of a healthy nervous system. Psychiatric manifestations can present due to low serum B₁₂ levels in the absence of other well-recognized neurologic and hematologic abnormalities. Many psychiatric disorders including dementia, depression, psychosis, schizophrenia, alcohol

dependence, mania and obsessive-compulsive disorder are associated with vitamin B₁₂ deficiency [41, 42]. Some investigators have reported the prevalence of low serum vitamin B₁₂ levels among psychiatric inpatients to be between 5% and 30% [43]. The high prevalence of low vitamin B₁₂ levels could possibly be a result of genetics, patients' feeding habits or dietary deficiencies resulting from the mental illness [44]; use of anticonvulsants is also a possible cause [45].

Although we did not measure serum homocysteine concentrations, several authors have investigated plasma homocysteine concentrations in schizophrenic patients with conflicting results [46-49]. Adler-Nevo et al. [46] found increased plasma homocysteine concentrations in adolescent patients with schizophrenia, which was almost entirely attributed to the subgroup of male patients. Conversely, Virgos et al. [47] found no difference in plasma homocysteine levels in a sample of 210 patients with schizophrenia and controls. A study of 35 patients with chronic schizophrenia and 104 control subjects also showed no association between plasma homocysteine and schizophrenia [48]. Investigators proposed that schizophrenia was associated with a disturbance in folate metabolism independent of homocysteine levels. Another study suggested that homocysteine levels in female patients with schizophrenia were not significantly different from levels in patients with depression or dementia [49].

The mechanisms underlying the association of homocysteine with schizophrenia may involve the glutamatergic system. Homocysteine acts as a partial antagonist on N-methyl-D-aspartate glutamatergic receptors [50], which are implicated in schizophrenia. Moreover, homocysteine-lowering interventions (by the administration of vitamins) have recently been shown to improve symptoms in patients with chronic schizophrenia who also have hyperhomocysteinemia.

There is a known link between elevated plasma homocysteine levels and premature coronary and carotid atherosclerosis. Homocysteine is controlled both by mutations in its regulating enzymes and by B vitamins, folic acid, B₁₂ and B₆ (pyridoxine) [51, 52]. Some studies have reported that carotid intima-media thickness

might be reduced by vitamin B₁₂ supplementation in patients at high cardiovascular risk [53].

It has been proposed that poor nutrition, especially low B₁₂ intake, influence plasma homocysteine levels. Other factors such as caffeine and alcohol consumption [54], smoking [55], and a polymorphism in the gene for methylenetetrahydrofolate reductase, an essential enzyme in homocysteine metabolism [56], have been associated with high homocysteine plasma levels. In a sample of 258 patients with schizophrenia, the variables predicting homocysteine levels were gender, plasma folate and B₁₂ levels, mean red blood cell corpuscular volume and diastolic blood pressure [57].

Hyperhomocysteinemia is widely recognized as a risk factor for cardiovascular complications. Growing evidence suggests increased homocysteine concentrations in schizophrenic patients. Some authors suggest that it is primarily young males with schizophrenia who have elevated homocysteine concentrations [58]. Recently, Geller et al. [59] have found that siblings of patients with schizophrenia may present elevated homocysteine concentrations.

Female subjects have lower plasma homocysteine concentrations than males. This is compatible with findings supporting elevated homocysteine levels in the plasma of patients with chronic schizophrenia.

Previous studies investigating serum vitamin B₁₂ levels in patients with schizophrenia have had conflicting results. Saedisomeolia et al. [17] observed elevated serum vitamin B₁₂ levels in the group of patients with schizophrenia. Similarly, García-Miss Mdel et al. [18] reported that serum vitamin B₁₂ levels in patients with schizophrenia were higher than in the control group. In contrast, Silver et al. [19] reported lower vitamin B₁₂ levels among patients with schizophrenia; this finding was comparable with our results. Furthermore, some studies have found that serum vitamin B₁₂ levels were similar in schizophrenic patients and controls [20, 60].

Although previous studies reported lower serum vitamin B₁₂ levels in females than males [61-63], we observed no difference between genders. Estrogen may have a protective effect against elevated vitamin B₁₂ levels [64, 65].

Information on MPV levels in patients with schizophrenia is very limited. A recent cross-sectional study noted elevated MPV levels in patients with schizophrenia, particularly in patients exposed to atypical antipsychotics. More recently, Lee et al. [66] found high MPV levels in patients with schizophrenia and related psychoses, which were unaltered after 1 year of clozapine treatment. In the current study, MPV levels were higher in patients with schizophrenia than in control subjects; however, the difference was not statistically significant. We assume the small sample size is the cause for the lack of statistical significance.

RDW has been shown to be a predictor of mortality in the general population [67]. Several studies have demonstrated that higher RDW levels, even within the normal reference range, were associated with negative clinical outcomes in patients with heart failure, coronary artery disease, pulmonary hypertension, diabetes mellitus, Alzheimer's disease, stroke, and obesity [68]. To our knowledge, RDW levels in patients with schizophrenia have not yet been investigated. In the present study, we observed a statistically significant increase in RDW levels in patients with schizophrenia compared with control subjects. This is the first study to evaluate RDW levels in patients with schizophrenia.

A number of limitations should be acknowledged for the interpretation of our results. First, the sample size of the study was small. Second, we did not assess our subjects for other confounding factors such as smoking status, body mass index or illness duration. Third, our sample included patients with chronic schizophrenia receiving antipsychotic treatment. While we did not examine the role of antipsychotic treatment in mediating plasma homocysteine concentrations, it has been shown that usage of different antipsychotics does not influence the levels of homocysteine [69, 70]. Finally, pernicious anemia is a known risk factor for low serum levels of vitamin B₁₂ [71]; however, in this study, we did not use the anti-intrinsic factor antibody test to assess for this condition.

Conclusions

Our results demonstrate that patients with schizophrenia have increased RDW and MPV

levels along with decreased B₁₂ levels. Therefore, we suggest that high MPV and RDW levels may be associated with low vitamin B₁₂ levels in patients with schizophrenia. According to our study results, increased inflammation may play a pathophysiological role in the development of atherosclerosis in patients with schizophrenia. We recommend that patients with schizophrenia should be screened for possible low serum vitamin B₁₂ levels. Prospective clinical studies are necessary to confirm these findings.

Disclosure of conflict of interest

None.

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