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ASSOCIATION OF ERYTHROCYTE SEDIMENTATION RATE AND FIBRINOGEN CONCENTRATION WITH METABOLIC SYNDROME IN SCHIZOPHRENIC PATIENTS

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SUMMARY

Introduction: *Inflammation can be a process significant to the development of schizophrenia and metabolic disorders that are frequently found in patients suffering from schizophrenia. The aim of this study was to determine the values of erythrocyte sedimentation rate and fibrinogen concentration and to establish their possible association with MS and its components in schizophrenic patients.*

Subjects and methods: *A cross-sectional study was conducted on 200 subjects who were divided into two groups. The study group consisted of schizophrenic patients from the University Clinical Hospital Mostar (n=100), while the control group consisted of healthy subjects who came for systematic medical examinations at the infirmary of the Health Center Mostar (n=100). The diagnosis of MS was made according to NCEP-ATP III criteria, and on that basis subjects from both groups were divided into two subgroups, one with and one without MS. Inflammatory indicators that were determinated were erythrocyte sedimentation rate and fibrinogen concentration.*

Results: *Statistically, MS was significantly more frequent in schizophrenic subjects (46.0%) compared to the control group (29.0%) (p=0.013). Schizophrenic subjects with MS had statistically higher sedimentation rate and fibrinogen concentration compared to the schizophrenic subjects without MS, as well as compared to the control subgroup without MS. The most significant correlations discovered were for the relation of sedimentation rate with systolic (r=0.41) and diastolic (r=0.34) blood pressures.*

Conclusion: *Routine monitoring of erythrocyte sedimentation rate and fibrinogen concentration might have an important role in forecasting MS development and consequent adverse cardiovascular events which are the leading cause of mortality in schizophrenic patients.*

Key words: *erythrocyte sedimentation - fibrinogen - metabolic syndrome - schizophrenia - inflammatory processes*

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INTRODUCTION

It has been well known for decades that schizophrenic pateints have a reduced life span in comparison to general population (Newman & Bland 1991). The most important cause of increased mortality in schizophrenic patients is cardiovascular diseases, whose higher frequency is connected with an increased prevalence of metabolic syndrome (MS) in these patients (Monteleone et al. 2009). MS consists of several metabolic abnormalities and is, according to some studies, characterized by a mild chronic inflammatory state (Devaraj et al. 2009). Additionally, evidence on the role of inflammation and inflammatory processes in the etiopathogenesis and psychopatology of schizophrenia, as well as in other psychoses, is becoming more frequent. Therefore, inflammation can be explained as a process important to the development of schizophrenia and to the development of various metabolic disorders in schizophrenic patients (Fan et al. 2007). Despite the fact that increasingly more evidence on inflammation as a common characteristic of schizophrenia and metabolic disorders in schizophrenic patients exists, the association between inflammatory processes, MS and schizophrenia has yet to be fully explained (Leonard et al. 2012).

Fibrinogen is a plasma protein of the acute phase response that is created in hepatocytes, and plays a primary role in the coagulation process. It is considered that higher fibrinogen concentrations may be significantly associated with MS, and that this presents an independent risk factor for the development of cardiovascular disease (Ernst 1994, Ford 2003, Ma et al. 2010). Erythrocyte sedimentation rate is used as an indirect measure of the concentration of acute phase proteins, and its main determinants are gender, and the concentration of fibrinogen, hemoglobin, globulin and triglycerides (Steinvil et al. 2008). Erythrocyte sedimentation rate is claimed to be a long-term independent predictor of coronary heart disease development in persons of both genders, and to correlate significantly with a number of MS components (Andresdottir et al. 2003, Mardi et al. 2005).

Even though several current studies have confirmed a positive association between fibrinogen concentration and sedimentation rate with the presence of MS and its components, relations between these inflammatory indicators and separate MS components are yet to be

fully explained. The aim of this study was to determine the values of erythrocyte sedimentation rate and fibrinogen concentration and to establish their possible association with MS and its components in schizophrenic patients.

SUBJECTS AND METHODS

A cross-sectional study was conducted on 200 subjects divided into two groups. The study group consisted of schizophrenic patients from the University Clinical Hospital Mostar (n=100), while the control group consisted of healthy subjects who came to systematic medical examinations for various reasons (health clearances for drivers licenses, employment, and systematic examinations of employees) at the infirmary of the Health Center Mostar (n=100). Excluding criteria for both groups were as follows: the presence of autoimmune, degenerative, rheumatic, acute or chronic infectious diseases, malignancy, pregnancy, alcoholism, and drug addiction. Persons previously diagnosed with any of the MS components (hypertension, dyslipidemia, diabetes, obesity) were excluded from the control group. The groups were comparable by gender and age range (subjects of both genders, age 18-70 years). The diagnosis of schizophrenia was made according to diagnostic criteria from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (WHO 1996) by an experienced psychiatrist. The diagnosis of MS was made according to NCEP-ATP III criteria (Expert panel JAMA 2001), and on that basis the subjects from both groups were divided into two subgroups, one with and one without MS. All subjects signed an informed consent form after receiving a detailed description of the research prior to their involvement in the research.

Arterial blood pressure was measured by a mercury sphygmomanometer. Waist circumference was measured by tailor tape at navel level on the skin following expiration. All measurements were performed three times in succession and the medium value was subsequently calculated.

Blood samples were collected from all subjects at 8:30 a.m. after a 12 hour overnight fast. Biochemical parameters determined in blood serum were glucose, triglycerides and HDL cholesterol concentrations. The values obtained were determined by enzyme method immediately after collecting blood samples by means of a commercially available reagent (Olympus Diagnostic, GmbH, Hamburg, Germany) on an Olympus AU 600 automatic analyzer. The inflammatory indicators that were determinated were erythrocyte sedimentation rate and fibrinogen concentration. Erythrocyte sedimentation rate was determined separately on graduated pipettes from full blood samples with 3.8% sodium citrate as an anticoagulant, using the Westergreen method. Results were expressed in mm/h, and elevated levels were considered to be those above 13 mm/h (for men aged 20-50), 23 mm/h (for men over 50), and levels above 24 mm/h (for women aged 20-50), 28 mm/h (for women over 50). Fibrinogen concentration was determinated in citrated plasma samples applying the turbidimetric method and reference intervals 1.8-3.5 g/L for both genders.

Differences in the frequency of categorical variables were tested by Chi square (χ^2) test. In testing the differences in values of sedimentation rate and fibrinogen concentration as continuous variables, the Student t-test was used for normally distributed and the Mann-Whitney test for asymmetrically distributed results. For testing the differences in values of the examined inflammatory indicators in schizophrenic subjects with MS in comparison to schizophrenic subjects without MS and control groups, a two-way analysis of variance was used. For the subsequent determining of differences between the four separate subgroups a Scheffe post-hoc test was used. The Pearson correlation test was applied for testing correlations between the examined variables. A probability level of $p<0.05$ was considered statistically significant. SPSS statistic software, version 17 (SSPS Inc., Chicago, IL), as well as Statistic version 7.0 (StatSoft Inc., Tulsa, OK, USA) were used for all statistic analyses.

RESULTS

Statistically, MS was significantly more frequent in schizophrenic subjects (46.0%) compared to the control group (29.0%) ($p=0.013$).

Table 1 shows the frequency of elevated values of sedimentation rate and fibrinogen concentration in the study group and control group. Statistically, schizophrenic subjects had a significantly more frequently elevated fibrinogen concentration compared to the control group ($\chi^2=8.029$; $p=0.005$), while the study group and control group did not differ statistically significantly in the frequency of elevated values of sedimentation rate.

Statistically, schizophrenic subjects had a significantly more frequent higher average fibrinogen concentration (Student t-test=4.043; $p<0.001$) compared to the control group, while the study group and control group did not differ statistically significantly in average values of sedimentation rate (Mann-Whitney U test=0.674; $p=0.500$) (Table 2).

After dividing the group of schizophrenic subjects and control group into subgroups with and without a MS diagnosis, the values of sedimentation rate and fibrinogen concentration were compared separately between the new subgroups (Table 3).

Table 1. Frequency of elevated values of sedimentation rate and fibrinogen concentration in the study group and control group

Variable N (%)	Group		χ^2	p
	Schizophrenia	Control group		
Erythrocyte sedimentation	10 (10)	15 (15)	1.143	0.285*
Fibrinogen	57 (57)	37 (37)	8.029	0.005*

*χ^2 test; †Fisher's exact test

Table 2. Differences in sedimentation rate and fibrinogen concentration values between the study and control group

Variable (X±SD)	Group		t^a/z^b	p
	Schizophrenia	Control group		
Erythrocyte sedimentation	11.27±7.77	13.21±10.86	0.674	0.500[a]
Fibrinogen	3.77±1.05	3.26±0.69	4.043	<0.001[b]

[a] Mann-Whitney U test; [b]Student t-test

Table 3. Differences in erythrocyte sedimentation rate and fibrinogen concentration between subgroups of schizophrenic and control subjects with and without MS

Inflammatory indicator	Group	MS diagnosis		F	p
		YES	NO		
		M±sd			
Erythrocyte sedimentation	Schizophrenia	15.8±8.35	7.4±4.54	2.206	0.139[a]
	Control group	16.1±7.71	10.5±8.58	38.254	<0.001[b]
Fibrinogen	Schizophrenia	4.06±1.11	3.52±0.92	10.839	0.001[a]
	Control group	3.63±0.55	3.11±0.68	17.579	<0.001[b]

[a]differences between the subgroups of schizophrenic subjects and control subgroups
[b]differences between the subgroups with and without MS

Erythrocyte sedimentation rate did not differ significantly between the subgroups of schizophrenic and control subjects (p=0.139), however, statistically significant differences were found between subgroups considering a MS diagnosis (p<0.001). By an additional analysis and application of Scheffe's procedure, it was determined that schizophrenic subjects with MS had statistically significantly higher erythrocyte sediment-tation rates compared to schizophrenic subjects without MS (p<0.001), as well as compared to the control subgroup without MS (p=0.003). The control subgroup with MS had statistically significantly higher erythrocyte sedimentation rates compared to the schizophrenic subgroup without MS (p<0.001), as well as compared to the control subgroup without MS (p=0.013). Schizophrenic subjects with MS had significantly higher fibrinogen concentrations compared to the subgroup of schizophrenic subjects without MS (p=0.020), as well as compared to the control subgroup without MS (p<0.001). There were no statistically significant differences in the fibrinogen concentrations between the two control subgroups (p=0.054), or between schizophrenic subjects with MS and the control subgroup with MS (p=0.219) (Table 3).

Table 4. Correlation of erythrocyte sedimentation rate and fibrinogen concentration with MS components in the group of schizophrenic subjects

	Erythrocyte sedimentation		Fibrinogen	
	r	p	r	p
Waist circumference	0.29	0.003	0.15	0.126
Systolic pressure	0.41	<0.001	0.27	0.007
Diastolic pressure	0.34	0.001	0.24	0.016
Serum glucose	0.12	0.244	-0.03	0.738
HDL	-0.01	0.888	0.16	0.122
Triglycerides	0.22	0.029	0.22	0.029
Metabolic syndrome (MS)	-0.54	<0.001	-0.26	0.009
Number of MS components	0.51	0.001	0.23	0.022

Table 4 displays the correlation of erythrocyte sedimentation rate and fibrinogen concentration with MS components in the group of schizophrenic subjects. Erythrocytes sedimentation rate correlated positively with waist circumference, systolic and diastolic pressure, triglycerides concentration, as well as with MS prevalence and a number of MS components. Fibrinogen concentration correlated positively with systolic and diastolic pressure, with triglycerides concentration, as well as with MS prevalence and a number of MS components.

The most significant correlations were determined for the relation between erythrocyte sedimentation rate with systolic (r=0.41) and diastolic (r=0.34) pressure. In addition, moderate correlations between sedimentation rate with MS (r=-0.54) and number of MS components (r=0.51) were determined (Table 4).

Sedimentation rate and fibrinogen concentration also significantly correlated mutually, which were expected results (r=0.49; p<0.001).

DISCUSSION

The Prevalence of the MS in schizophrenic subjects was significantly higher compared to healthy subjects, which confirms the results of several studies contemplating higher prevalence rates of MS in patients suffering from schizophrenia compared to the general population (Cohn et al. 2004, Lee et al. 2012). The prevalence of MS in schizophrenic subjects in this study was almost two times higher than the prevalence of MS in the general US population (Ford et al. 2002). The importance of this increased prevalence of MS in patients suffering from schizophrenia is bolstered by the fact that MS increases the incidence of cardiovascular disease, and leads to higher morbidity and mortality in this group of patients (Jacob & Chowdhury 2008).

Schizophrenic subjects had significantly higher average fibrinogen concentrations and a significantly higher frequency of elevated fibrinogen concentration compared to subjects in the control group. These results are in accordance with the results of research conducted in Belgium, in which schizophrenic subjects had significantly higher plasma fibrinogen concentrations in comparison to healthy subjects (Maes et al. 1997).

Results regarding differences in sedimentation rate between subgroups with and without MS showed significantly higher values of sedimentation rate in subgroups with MS comparing to subgroups without MS, suggesting a significant influence of MS on values of erythrocyte sedimentation rate with reference to the influence of schizophrenia. On the other hand, results regarding differences in fibrinogen concentration between subgroups with and without MS suggest the influence of schizophrenia and MS on increasing plasma fibrinogen concentration in patients suffering from schizophrenia. As no studies known to us have considered the association between sedimentation rate or fibrinogen concentration with MS in schizophrenic subjects, our results were not comparable with results of other similar studies on schizophrenic patients. The most significant correlations in the group of schizophrenic subjects were found between erythrocyte sedimentation rate and the values of systolic and diastolic blood pressures. Results that demonstrate a strong correlation between systolic and diastolic pressure and sedimentation rate might potentially have everyday clinic significance by highlighting the correlation between blood pressure and intensity of inflammatory processes, which can be found in the background of MS development in patients suffering from schizophrenia. Blood pressure should therefore be monitored more closely in schizophrenic patients with higher values of erythrocyte sedimentation rate.

According to some studies on the general population, waist circumference is an MS component that has the most significant correlations with inflammatory indicators and among them with sedimentation rate and fibrinogen concentration (Rogowski et al. 2010). In schizophrenic subjects from our study, waist circumference correlated significantly only with sedimentation rate, but not with fibrinogen concentration. Considering that waist circumference is a clinical measure of abdominal obesity, our results show that abdominal obesity in schizophrenic patients is associated significantly with sedimentation rate, but not with fibrinogen concentration.

Sedimentation rate and fibrinogen concentration correlated positively with the prevalence of MS and with a number of MS components, and this is in accordance with the previous study, which among other things, demonstrated the existence of a significant correlation between a number of MS components, sedimentation rate and fibrinogen concentrations (Andresdottir et al. 2003). Results regarding the correlation of plasma fibrinogen with MS and MS components corroborate the results of Imperatore et al. on the general population, who found that fibrinogen concentration and the frequency of hyperfibrinogenemia increased progressively as number of MS components increased (Imperatore et al. 1998).

CONCLUSION

Our results suggest that erythrocyte sedimentation rate has a more significant association with MS and its components, while fibrinogen concentration is associated with MS and schizophrenia. Considering the existence of a positive correlation between these inflammatory indicators and MS prevalence in schizophrenic patients, their routine monitoring may be important in forecasting MS development and consequential adverse cardiovascular events which are the leading cause of mortality in this population.

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