

## METABOLIC SYNDROME AND INFLAMMATION MARKERS IN PATIENTS WITH SCHIZOPHRENIA AND RECURRENT DEPRESSIVE DISORDER

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### SUMMARY

**Background:** The high prevalence of metabolic syndrome in patients with psychiatric disorders, almost double the prevalence reported for the general population, is worrying. The aim of this study is to investigate the presence of metabolic syndrome and inflammatory marker levels in patients with schizophrenia and recurrent depressive disorder in a Croatian psychiatric sample.

**Subjects and methods:** This study included 62 inpatients with schizophrenia and 62 with recurrent depressive disorder treated at the Department of Psychiatry, University Hospital Centre Split, enrolled from November 2011 until May 2012. The cases were compared to 124 healthy subjects from the general population.

**Results:** The presence of metabolic syndrome was found in 56.5% of the patients with schizophrenia and 53.2% of the patients with depression, which was significantly more prevalent than in the control group (32.3%). The levels of inflammation markers (i.e., C-reactive protein and PAI-1) were significantly higher among patients with metabolic syndrome.

**Conclusions:** Patients with schizophrenia and recurrent depressive disorder demonstrate a high prevalence of metabolic syndrome that is also related to inflammation processes. In the context of integrative medicine, clinicians and researchers should consider psychiatric patients within a holistic approach.

**Key words:** schizophrenia - recurrent depressive disorder - metabolic syndrome - inflammation markers – CRP - PAI-1

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### INTRODUCTION

Comorbidity and multimorbidity represent one of the greatest challenges to academic and clinical medicine. Many disorders are often comorbidly expressed in diverse combinations (Jakovljević & Ostojić 2013). Major mental disorders like schizophrenia and major depressive disorder (MDD) have been associated with many traditional cardiovascular risk factors: elevated blood pressure, obesity, atherogenic dyslipidemia, increased prevalence of diabetes, alcohol and substance abuse, heavy smoking and low physical activity. Interaction of stress, psychotrauma, hypercortisolemia and immune function disorders are known to contribute or associate with development of both metabolic syndrome and above-mentioned mental disorders (Jakovljević et al. 2007, Maslov et al. 2008).

It is well known that serotonergic system is mostly associated with depression, but also with food intake, pain sensation, sleep regulation, aggression and stress response, reproduction and autonomic functions relevant to metabolism, such as blood pressure, cardiovascular control, pancreatic function (Silić et al. 2012). This is obvious in the link between metabolic syndrome (MS) which has been inversely correlated to serotonin (Horacek et al. 1999). However, the issue of MDD being the cause, the consequence or just a simple

indicator of the MS is still unresolved (Jakovljević et al. 2007).

Patients with mental disorders such as schizophrenia, or at least some subgroups, have an increased prevalence of MS and its components, risk factors for cardiovascular disease and type 2 diabetes (Marčinko et al. 2008). Although the prevalence of obesity and other risk factors such as hyperglycemia are increasing in the general population, patients with major mental illnesses have an increased prevalence of overweight and obesity, hyperglycemia, dyslipidemia, hypertension, smoking and substantially greater mortality, compared with the general population. Persons with major mental disorders lose 25 to 30 years of potential life in comparison with the general population primarily due to premature cardiovascular mortality. The causes of increased cardiometabolic risk in this population can include nondisease-related factors such as poverty and reduced access to medical care, as well as adverse metabolic side effects associated with psychotropic medications, such as some antipsychotic drugs. Individual antipsychotic medications are associated with well-defined risks of weight gain and related risks for adverse changes in glucose and lipid metabolism (Newcomer 2007).

Depression is associated with increased physical morbidity and overall mortality (Koponen et al. 2010). Although reports have suggested that depression may

lead to the development of cardiovascular disease through its association with the metabolic syndrome; however, little is known about the relationship between depression and the MS (Kinder et al. 2004, Jakovljevic et al. 2007). Recent studies suggest comorbidity between MDD and MS (Vancampfort et al 2014). For both disorders, impaired serotonergic neurotransmission and inflammatory processes have been suggested (Silić et al. 2012, Newcomer 2007), while some authors advocate anti-inflammatory therapeutic approaches in both depression and schizophrenia (Mueller 2013, Young et al. 2014). Beside co-morbid somatic illness, somatic symptoms may appear as a result of side effects of antipsychotics during treatment of psychotic disorders, which may lead to certain diagnostic problems in deciding regarding the origin of such symptoms (Kozumplik et al. 2009).

Given the abovementioned clinical implications of metabolic syndrome in psychiatric patients, the aim of this study was to assess the presence of MS in patients with schizophrenia and recurrent depression, in comparison to a healthy control group. Furthermore, we investigated the relations between MS and several inflammatory factors among psychiatric patients.

## **PATIENTS AND METHODS**

### **Patients**

Three groups were involved in this case-control study. The first cases group was made up of patients with diagnosed recurrent depressive disorder (RDD) without psychotic features. The second cases group was made of the patients with diagnosed schizophrenia. Both cases groups were enrolled from the Department of Psychiatry University Hospital Centre Split, as consecutive cases from November 2011 until May 2012. The diagnosis of both RDD and schizophrenia were made according to the diagnostic criteria of the International Statistical Classification of Diseases and Related Health Problems, 10<sup>th</sup> Revision, confirmed by two independent psychiatrists.

The third study group was made of controls from the “10 001 Dalmatians” research program. Research program “10 001 Dalmatians” collects biomedical information from meta-populations on Adriatic area of Croatia, for genetic epidemiological research and development of the largest research-oriented biobank in Croatia (Polašek 2013). For purposes of this study, subjects from the Split cycle were involved. There were 1 012 subjects from the general population, amongst which a total of 150 were randomly selected to serve as the controls for the two groups of cases. Only 124 healthy subjects without any indication of the psychiatric diseases were sub-selected.

Oral and written information about the study was provided to all patients and controls, and their consent was obtained before participation. The study received

appropriate ethical approvals from the Human Research Ethics Committee of the University Hospital Centre Split (patients) and the Human Research Ethics Committee of Medical School of the University of Split (controls).

### **Measures**

Socio-demographic data on patients were collected by a general questionnaire (age, sex, somatic anamnesis). General questionnaire for patients contained questions to collect data related to the disease: diagnosis, current treatment, hospitalizations and duration of illness.

Diagnosis of the diseases was determined from the Medical history and through a specialist psychiatric examination of each patient in accordance with ICD-10. The research included the patients hospitalized on the Department of Psychiatry at the University Hospital Centre Split, on the acute ward due to relapse in clinical appearance that is the recurrence of a depressive or schizophrenic episode, and as a result of noncompliance in therapy, insufficient therapy and natural course of disease. The patients with the anamnesis of residual type of the disease were not included in the research.

### **Biological parameters**

The diagnosis of MS was defined according to the American National Institute of Health, Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults criteria (NCEP ATP III), which require the presence of three or more of the following five criteria: 1) increased waist circumference: >88 cm in women or >102 cm in men; 2) elevated triglycerides:  $\geq 1.7$  mmol/L; 3) reduced high-density lipoprotein (HDL) cholesterol: <1.03 mmol/L in men or <1.29 mmol/L in women; 4) elevated blood pressure:  $\geq 130/85$  mm/Hg; 5) elevated fasting glucose:  $\geq 5.6$  mmol/L.

Weight, height and waist circumferences (measured in duplicate at the level with the navel in thin subjects) were measured with an accuracy of 0.1 kg and 0.5 cm. Body mass index was calculated using the formula:  $\text{weight}[\text{kg}]/(\text{height}[\text{m}])^2$ . Blood pressure was measured by using a random zero sphygmomanometer in supine position from the right arm after fasting for 12 hours.

All venous blood samples were drawn from the right antecubital vein after fasting for 12 hours. The levels of glucose in plasma were determined from the sample of capillary blood in the morning between 8 and 9 a.m. at least 2 hours after the meal. Plasma glucose concentrations were analyzed enzymatically with a clinical chemistry analyzer (“Abbott Architect 8200”). The number of leukocytes in the peripheral blood was analyzed with a haematological analyzer “Siemens ADVIA 2120”. Serum concentration of total

cholesterol, triglycerides and uric acid were measured using fully enzymatic commercial „Abbott diagnostics“ kits with an “Abbott Architect 8200” analyzer. Low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL), were measured by commercial tests from the company „Roche“. Cortisol and ACTH in the serum were determined by the chemiluminescent method on the analyzer „Roche“ COBAS e601 in the morning and afternoon sample. C-reactive protein (CRP) was measured by the automated analyzer using a latex turbidimetric immunoassay “Abbott” commercial kits. With the analyzer BCS „Siemens“ for coagulation tests the PAI-1 levels were determined. The levels of HbA1c were measured with the “Roche” commercial test on the analyzer COBAS INTEGRA 400 plus. All biochemical analyses were performed at the Department of Medical Laboratory Diagnosis of the University Hospital Centre Split. The laboratory is certified for performing all of the stated analyses and is under supervision of Croatian Society for Clinical Chemistry through quality control for the stated analyses.

### Statistical analysis

The analysis was based on both parametric and non-parametric methods, depending on the data distribution. We used Kolmogorov-Smirnov test to infer the data distribution type. In case of normal distribution, mean and standard deviation (SD) of the numerical variables were used, followed by the unpaired Student t-test and chi square tests were used for group comparison (with Fisher’s exact test used in situation with a small number of cases for a Chi-square test). For variables that did not follow the normal distribution Mann-Whitney test was used. Similarly, we employed either Pearson correlation coefficient (for variables with normal distribution), or the Spearman rank correlation test (for variables with non-normal distribution).  $P < 0.05$  is considered signi-

ficant. Statistical analysis was performed using the statistical package SPSS version 15.0. (SPSS Inc., Chicago, IL, USA).

### RESULTS

This study was based on total of 124 patients divided in two equal groups, one with schizophrenia and the other with depression. In addition, we used a total of 124 controls from the general population. The initial analytic step indicated a certain level of differences between analyzed groups (Table 1).

The results of this study disclose comparative prevalence of metabolic syndrome among patients with schizophrenia and depression. The prevalence of metabolic syndrome according to NCEP-ATPIII criteria was 56.5% for the patients with schizophrenia, 53.2% among the patients with depression and 32.3% among individuals in the control group, which was statistically significant (Table 2;  $P = 0.002$ ). Furthermore, a detailed analysis of each disease involved in metabolic syndrome showed a statistically significant difference (Table 3).

The patients with depression had higher morning and evening cortisol levels in comparison to the group of patients with schizophrenia. Furthermore, patients with schizophrenia showed higher diurnal cortisol oscillation than did the patients with depression (Table 3).

The patients with and without metabolic syndrome had different serum levels of PAI-1 regardless of their psychiatric diagnosis (depression or schizophrenia). The patients with depression had statistically lower values of PAI-1 than individuals without metabolic syndrome, while simultaneously having lower levels of CRP-a (Table 3). The patients with schizophrenia had only one statistically significant difference, lower level of PAI-1 among patients with no metabolic syndrome (Table 3).

**Table 1.** Basic comparison of subjects with depression, schizophrenia and controls

	Depression (n=62)		Schizophrenia (n=62)		Controls (n=124)		P	Pair-wise differences*
	Mean±SD	Min-max	Mean ±SD	Min-max	Mean ±SD	Min-max		
Age (years)	54.95±10.23	21-74	42.09±10.77	19-65	53.18±11.29	19-74	<0.001	1-2,2-3
Gender, men; n (%)	21 (33.9)	-	39 (62.9)	-	77 (62.1)	-	<0.001	1-2,1-3
Height(cm)	174.41±8.58	156-194	176.55±9.88	151-195	176.28±7.62	162-194	0.214	-
Weight (kg)	78.78±14.75	50-120	87.66±20.43	43-135	81.71±17.33	61-117	0.006	1-2,2-3,1-3
Body mass index (kg/m <sup>2</sup> )	26.77±4.40	17.51-37.04	28.05±6.08	14.37-44.98	26.76±5.08	18.21-34.04	0.072	-
Waist circumference (cm)	95.72±14.14	66-124	101.38±16.94	60-135	89.14±12.98	72-126	0.060	-
Systolic blood pressure (mmHg)	128.28±16.26	90-160	126.52±17.42	90-170	127.29±18.30	92-184	0.609	-
Diastolic blood pressure (mmHg)	81.81±10.63	60-105	80.89±13.59	60-120	81.05±12.41	58-118	0.623	-
Heart rate (min <sup>-1</sup> )	76.55±7.89	60-100	78.95±9.87	58-100	77.14±8.26	54-96	0.340	-

\*1-patients with RDD; 2-patients with schizophrenia; 3-healthy controls

**Table 2.** Prevalence of metabolic syndrome and its individual components in three analyzed groups

Variable	Depression (n=62)	Schizophrenia (n=62)	Controls (n=124)	P*			
				Across groups	dep-sch	dep-con	sch-con
Abdominal adiposity	39 (62.9)	36 (58.1)	52 (41.9)	0.012	0.582	0.007	0.038
Hypertriglyceridemia	39 (62.9)	32 (51.6)	48 (38.7)	0.006	0.204	0.002	0.094
Low HDL	17 (27.4)	37 (59.7)	32 (25.8)	<0.001	<0.001	0.814	<0.001
Hypertension	32 (51.6)	24 (38.7)	35 (20.2)	0.007	0.149	0.002	0.148
Elevated glucose	35 (56.5)	22 (35.5)	29 (23.4)	<0.001	0.019	<0.001	0.081
Metabolic syndrome	35 (56.5)	33 (53.2)	40 (32.3)	0.002	0.718	0.002	0.006

\*P values represent the level of statistical significance in comparison of the entire studied population, comparison between groups; 1-2 depicts comparison of the patients with depression with the patients with schizophrenia; 1-3 depicts the comparison of the patients with the control group; 2-3 depicts comparison of the schizophrenic patients with the control group

**Table 3.** Comparison of markers of inflammation in cases with depression and schizophrenia, according to presence of metabolic syndrome

	Depression			Schizophrenia			MS*	
	MS (n=19)	without MS (n=26)	P	MS (n=21)	without MS (n=23)	P	Yes P	No P
PAI-1	2.56±1.96	1.39±1.29	0.041	2.96±1.94	1.85±1.17	0.027	0.465	0.128
CRP	7.09±6.21	4.92±5.68	0.012	7.01±5.91	5.13±3.68	0.263	0.850	0.719
ACTH	6.67±4.72	8.27±5.43	0.489	7.34±6.92	7.89±4.31	0.252	0.204	0.621
Morning cortisol	492.5±183.1	527.9±155.4	0.611	500.9±160.9	530.7±132.7	0.918	0.942	0.883
Evening cortisol	288.2±193.8	269.8±212.5	0.492	227.2±129.8	195.4±91.9	0.141	0.039	0.001

\*The last two columns are comparisons of subgroups with either diagnosed metabolic syndrome or not diagnosed, between cases with depression and schizophrenia

## DISCUSSION

One of the main outcomes of this study is awareness that schizophrenia and depression require systematic approach, rather than a solely psychiatric treatment scheme. In addition, both subgroups seem to suffer increased burden of metabolic syndrome. Although that can be at least partly attributable to medication scheme, it nevertheless shows the need for metabolic screening and adequate control of somatic symptoms in these patients.

Metabolic syndrome is a cluster of symptoms with higher prevalence in psychiatric patients compared to general population (Vuksan-Ćusa et al. 2014, Oreški et al. 2012). The components of MS has clearly increased over the past decade throughout the developed world. The CATIE trial reported that 33.2% of the 1448 patients with schizophrenia had hypertension, 10.4% diabetes mellitus, 47.3% dyslipidemia when defined by elevated serum triglycerides and 48.3% when defined as low serum HDL (Nasrallah et al. 2006). The similarity of these results suggests that these figures can be considered as generalizable, and therefore further supports the statements from this study. In addition, other studies (Iacovides et al. 2008, Jukić et al. 2009) have also reported increased prevalence of diabetes mellitus, cardiovascular disease, hypertension, obesity and metabolic syndrome in patients with schizophrenia.

The prevalence of metabolic syndrome according to NCEP-ATPIII criteria in our study was 56.5% for the

patients with schizophrenia, 53.2% among the patients with depression and 32.3% among individuals in the control group, what was rather higher than e.g. estimated prevalence of MS in the US population of 23.7%, ten years ago (Ford et al. 2004). The prevalence of metabolic syndrome among Australian patients was 54% overall, among patients with schizophrenia 51% and 46% among patients with major depression with psychotic symptoms (John et al. 2009). Kinder et al. (2004) pointed out the gender difference and strong association between depression and the MS in women, while in men the association was much weaker and did not reach statistical significance. Depression was not associated with any individual components of the MS in men, and in fact the direction of the relationship appeared to be reversed for triglyceride and HDL cholesterol levels. Similar data about gender difference between schizophrenia and the MS does not exist. In our study the group of depressed patients consisted of the majority of women (66.1%), compared to patients with schizophrenia (37.1%) and controls (37.9%), and that might be the reason of higher prevalence of MS in the group of depressed patients.

The influence of age on the MS and its components also must be considered. When comparing these two groups of inpatients, we need to point out that depressed patients are 12.86 years older than patients with schizophrenia, but the prevalence of the MS is quite the similar. Alexander et al. (2008) explained the influence of age and body mass index on the metabolic syndrome and its components.

The findings in the study conducted by Topić et al. (2013) have shown that MS was present in 31.6% of MDD patients. This is in line with a study that found the prevalence of MS in depressed population to be 8% - 41%. The data on the relationship between depression and metabolic syndrome are very controversial due to inconclusive results, variations in study design, definitions of MS, evaluation of depressive symptoms or depressive disorder, and overlapping of recurrent depression and bipolar II disorder (Jakovljević et al. 2007). Some other studies have similar data about prevalence of MS, like Dunbar et al. (2008) and it was 30.4%.

The finding of this research concerning higher levels of inflammation protein CRP in depressed patients with metabolic syndrome is in the line with the study by Maes et al. (2011), who showed that increased inflammation with influence on lower serotonin levels, and metabolic abnormality in depression could be in the circle in which serotonin and proinflammatory cytokines are intertwined and mutually induce one another. Vuksan-Ćusa et al. (2010) found the presence of MS in 37% patients with schizophrenia and significant association between high CRP and the presence of MS; patients with high CRP had 2.153 times higher risk for MS. More recently, significant associations were found between CRP and two subcomponents of MS - waist circumference and diastolic blood pressure (Vuksan-Ćusa et al. 2013).

In this study, plasma levels of PAI-1 were also associated with features of metabolic syndrome among psychiatric patients. Depression is characterized by high PAI-1 levels, and conditions related to a hypofibrinolytic status, such as metabolic syndrome, are associated with an increased risk for both depression and cardiovascular events (Hoirisch-Clapauch et al. 2013). The present research was the first one in Croatia to investigate the role of the PAI-1 as the component of the MS in depression and schizophrenia, and our results were consistent with previous findings in the literature.

Some limitations of the present study warrant consideration. The cross-sectional design cannot obtain the temporal changes and causal relations, some crucial variable such as comorbidity onset could not be obtained. Differences in age between patients with schizophrenia and depression may contribute to the differences in comorbidity results. Patients with depression due to its better functioning may seek help for various somatic complaints more often than patients with schizophrenia. A larger sample size of the both groups, with longitudinal prospective follow up would be more beneficial.

## CONCLUSION

In the context of integrative medicine, clinicians and researchers should consider psychiatric patients within a holistic approach. Both schizophrenia and depression

appear to have strong and distinctive association with metabolic syndrome and related inflammation factors, requiring a revised and improved education and practice to adjust for these aspects of the apparently psychiatric diseases.

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