Prevalence of Metabolic Syndrome among Patients with Major Depressive Disorder – Differences Between Newly Diagnosed First Episode and Recurrent Disease

Rudolf Ljubičić[1], Hrvoje Jakovac[2], Ivana Ljubičić Bistrović[3], Tanja Frančeski[1], Ana Kovak Mufić[1] and Dalibor Karlović[1]

[1] University of Zagreb, University Hospital Center »Sestre milosrdnice«, Department of Psychiatry, Zagreb, Croatia
[2] University of Rijeka, School of Medicine, Department of Physiology and Immunology, Rijeka, Croatia
[3] University of Rijeka, University Hospital Centre Rijeka, Department of Psychiatry, Rijeka, Croatia

A B S T R A C T

The objective of the present study was to assess differences in prevalence of the metabolic syndrome among depressed patients in regard to the duration of the illness (first episode versus recurrent episodes). A total of 190 patients suffering from major depressive disorder were included in the study, diagnosed according to International classification of disorders, 10th revision[1]. The same criteria were used to divide participants into two groups: first episode major depressive disorder and major depressive disorder with recurrent episodes. The metabolic syndrome was defined according to the criteria of the American National Cholesterol Education Program-Treatment Panel III[2]. Results showed that metabolic syndrome is significantly more prevalent in patients with recurrent major depressive disorder (45.2%) compared to patients with first episode of major depressive disorder (27.3%), mainly due to differences in plasma glucose, triglycerides and HDL-cholesterol levels. These findings indicate the importance of the duration of depression and the number of recurring episodes as factors involved in etiopathogenesis of the associated metabolic syndrome.

***Key words**: major depressive disorder, first episode, recurrent, metabolic syndrome, NCEP-ATP III, prevalence*

Introduction

Metabolic syndrome is a clinical phenomenon that includes increased abdominal fat, increased fasting glucose levels with the development of insulin resistance, increased blood pressure and serum lipid disorders[3]. Patients with metabolic syndrome have an increased risk for the development of type II diabetes and cardiovascular disease[4]. Epidemiological data revealed a high incidence of metabolic syndrome among the psychiatric population[5,6]. The prevalence of metabolic syndrome in patients with major depressive disorder (MDD) ranges from 25 to more than 50%, depending on the study, population and criteria of diagnosing metabolic syndrome[6–13]. Several prospective cohort studies have clearly pointed to the depressive disorder as a predictor of metabolic syndrome development[14–16]. Moreover, prospective study that lasted for 15 years and included 4256 participants, as a part of Vietnam Experience Study, established that major depressive disorder predicts cardiovascular mortality after adjusting for a range of covariates[15].

Common development of the metabolic syndrome following depression is often attributed to the »unhealthy« lifestyle as part of depressive disorder[5,6]. Namely, lowered mood with an accompanying loss of libido and hypobulia usually influences patient habits, which then leads to a disbalance of bodily homeostasis and development of metabolic syndrome. Birth cohort study conducted by Gaysina and colleagues[14] found that early onset of depressive symptomatology (adolescence) is a strong predictor of obesity later in life, in comparison to the late onset of depression (adult age). However, so far it is not known whether there is any correlation between

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metabolic syndrome development and duration or severity of depression.

Considering these insights, the objective of present study was to assess differences in prevalence of the metabolic syndrome among depressed patients regarding the duration of the illness (first episode versus recurrent episodes).

Subjects and Methods

Subjects and diagnostic criteria

The MDD study group consisted of 190 patients, 44 with first episode MDD (F-MDD) and 146 with recurrent MDD (R-MDD). The F-MDD group included 28 males and 16 females. The R-MDD group included 87 males and 59 females. Sociodemographic and clinical parameters of all included subjects are presented in Table 1. All subjects with MDD were inpatients. The inclusion criteria for this study were the diagnosis of MDD, using the International classification of disorders, 10th revision (ICD-10)[1]. and the absence of any other psychiatric disorder (including anxious and somatization disorders and chronic fatigue syndrome). Patients with any use of psychoactive compounds including alcohol in their medical history were excluded from the study. Furthermore, patients that had taken any anti-inflammatory or anti-aggregation medicines, as well as statins, were also ex-

TABLE 1
DIFFERENCES IN SOCIO-DEMOGRAPHIC, CLINICAL AND LABORATORY CHARACTERISTICS BETWEEN STUDY GROUPS

	First episode MDD N=44	Recurrent MDD N=146	Control group N=242	Statistical analysis
Gender: N(%)				
Male	28 (63.6)	87 (59.6)	153 (63.2)	$\chi^2 = 0.564$
Female	16 (36.4)	59 (40.4)	89 (36.8)	df = 2, p = 0.754
Level of education: N(%)				
Elementary school	9 (20.5)	20 (13.7)	4 (1.7)	$\chi^2 = 110.590$
Medium expertise	20 (45.4)	108 (74.0)	82 (34.9)	df = 4, p < 0.01
High expertise	15 (34.1)	18 (12.3)	149 (63.4)	
Marital status: N(%)				
Married	30 (68.2)	107 (73.3)	147 (62.8)	$\chi^2 = 13.524$
Unmarried	11 (25.0)	26 (17.8)	78 (33.4)	df = 4, p < 0.01
Divorced/Widowed	3 (6.8)	13 (8.9)	9 (3.8)	
Employment status: N(%)				
Employed	21 (47.7)	59 (40.4)	203 (86.7)	$\chi^2 = 104.997$
Unemployed	14 (31.8)	38 (26.0)	24 (10.3)	df = 4, p < 0.01
Retired	9 (20.5)	49 (33.6)	7 (3.0)	
Residence: N(%)				
Urban	32 (72.7)	97 (66.4)	177 (75.3)	$\chi^2 = 3.536$
Rural	12 (27.3)	49 (33.6)	58 (24.7)	df = 2, p = 0.171
Age in years (mean±SD)	50.1 ± 12.7	52.5 ± 10.7	50.0 ± 10.5	F = 2.553 df = 2, p = 0.079
Systolic blood pressure (mean±SD)	125.7 ± 14.5	129.6 ± 13.5	127.2 ± 12.5	F = 1.797 df = 2, p = 0.168
Diastolic blood pressure (mean±SD)	77.1 ± 11.9	80.9 ± 10.7	80.1 ± 7.5	F = 2.305 df = 2, p = 0.102
Waist circumference (mean±SD)	93.7 ± 14.3	95.0 ± 13.4	94.3 ± 12.2	F = 0.161 df = 2, p = 0.852
BMI (mean±SD)	26.7 ± 3.9	27.6 ± 4.6	27.7 ± 4.0	F = 0.772 df = 2, p = 0.463
Cholesterol (mmol/L) (mean±SD)	5.9 ± 1.4	5.9 ± 1.4	5.9 ± 1.0	F = 0.027 df = 2, p = 0.973
Triglycerides (mmol/L) (mean±SD)	1.8 ± 1.6	2.3 ± 1.4	1.7 ± 1.1	F = 5.050 df = 2, p < 0.01
HDL-cholesterol (mmol/L) (mean±SD)	1.2 ± 0.3	1.4 ± 0.4	1.4 ± 0.3	F = 9.213 df = 2, < 0.01
LDL-cholesterol (mmol/L) (mean±SD)	3.7 ± 1.2	3.7 ± 1.1	3.7 ± 0.9	F = 0.024 df = 2, = 0.976
Glucose (mmol/L) (mean±SD)	4.8 ± 1.0	5.8 ± 1.9	5.4 ± 1.4	F = 6.804 df = 2, < 0.01

cluded. Exclusion criteria also included disorders that could be associated with MDD, such as neurological diseases, untreated hypothyroidism or poorly controlled diabetes mellitus, and immunological and autoimmune diseases. All investigated patients were screened for acute infection by body temperature measurement, erythrocyte sedimentation rate and leukocyte count[17]. All patients having increased body temperature over 36.7 °C, or a leukocyte count greater than 9×10^9/L, or an erythrocyte sedimentation rate greater than 10 mm/h were excluded from the study. None of the patients included in this study had taken any psychotropic medication for 30 or more days prior to the study. The control group consisted of 242 healthy subjects (153 males and 89 females), mostly hospital workers, medical students and voluntary blood donors, without any psychiatric or somatic disorders, alcohol or other drugs abuse, which was examined by self-report. Informed consent was obtained from all included subjects after a complete and extensive description of the study profile. The study was approved by Ethics Committee of the University Hospital Center.

The study included all patients that had been admitted for inpatient treatment with the diagnosis of MDD in the period from January 2010 to May 2012. All MDD patients presenting the above described exclusion criteria were excluded from the study. Upon meeting the inclusion criteria according to the described criteria for first and recurrent MDD based on ICD 10 criteria, patients were divided into the first episode MDD group and recurrent episode MDD group.

Variables of disease features (number of episodes, duration of MDD in years) were obtained from the structured clinical interview based on the Mini International Neuropsychiatric Interview (MINI)[18] and were performed by a trained psychiatrist. Body mass index (BMI) was calculated using the accepted formula (BMI=weight in kilograms/height in square meters). The diagnosis of metabolic syndrome was verified according to the criteria of the American National Cholesterol Education Program (NCEP) Treatment Panel III (ATP III)[1,4]. The NCEP ATP III defines metabolic syndrome as the presence of three or more of the following criteria: waist circumference >102 cm in men, >88 cm in women; hypertriglyceridemia <1.7 mmol/L; HDL-cholesterol >1.03 mmol/L in men, >1.29 mmol/L in women; blood pressure <130/85 mm Hg; and fasting glucose <5.6 mmol/L.

Biochemical measurements

Blood samples were taken from patients for the analysis of metabolic parameters. Blood samples were taken from the cubital vein in two vacuumed eprouvettes in the morning, after 12 h of fasting and after a 30 minute pause: one eprouvette without an anticoagulant for the determination of glucose and lipids.

Triglycerides, glucose and HDL cholesterol were determined with enzyme methods using commercial reagents (Olympus Diagnostics, Germany). In our laboratory, the value of the inter-assay CV was 4.4% 1.5% for glucose, 2.4% for triglycerides, and 2.1% for HDL cholesterol.

Statistical analyses

The normal distribution was assessed for all measures and for each group using the Kolmogorov-Smirnov test. Sociodemographic and clinical characteristics of patients and healthy control subjects were compared in frequencies using the Chi-square test and for continuous variables using analysis of variance (ANOVA) with Bonferroni post hock test for comparation between groups. Association of metabolic syndrome components with first episode or recurrent MDD was tested with logistic regression analysis where dichotomous dependent variable was first episode MDD and recurrent MDD. Statistical significance was based upon value of $\alpha=0.01$.

Statistics was done with SPSS software (SPSS for Windows 17.0, SPSS, Chicago, IL, USA).

Results

We found that prevalence of completely developed metabolic syndrome diagnosed according to ATP III criteria among patients with first MDD episode was 27.3%, whereas in those with recurrent disease prevalence was 45.2%. The analysis showed the existence of statistically significant differences between patients with first episode and recurrent MDD regarding plasma triglycerides, HDL and glucose concentrations (Table 1). The Post hock Bonferroni test was done to establish the reason of significant difference and between which groups.

The above mentioned significant difference in triglycerides occurred due to statistically significant differences in triglycerides' values in MDD patients with more depressive episodes and the control group ($p<0.01$). There is also a statistically significant difference in HDL cholesterol values between first episode and recurrent MDD ($p<0.01$), as well as between first episode MDD and the control group ($p<0.01$). Statistically significant differences were also observed in plasma glucose values between first episode and recurrent MDD ($p<0.01$).

The logistic regression was performed in order to examine the connection of first episode and recurrent MDD with values of the exact components of the metabolic syndrome according to ATP III criteria. In the group of the MDD participants, the model in which one or more episodes were correlate variable were statistically significant ($\chi^2=35.612$; df=6; $p<0.01$).

The model completely explains 19.2–28.2% (Cox & Snell $r^2=0.192$; Negelkerke $r^2=0.282$) and correctly qualifies 79,6 % of the cases (Table 2). HDL cholesterol and glucose values were significantly associated with recurrent MDD.

Discussion

In the present study, which included a total of 190 depressive inpatients, we found that prevalence of meta-

TABLE 2
LOGISTIC REGRESSION FOR THE GROUP OF MDD PATIENTS, WHERE ONE OR RECURRED EPISODES WERE DEPENDENT VARIABLES, WHILE SYSTOLIC BP, DIASTOLIC BP, WAIST CIRCUMFERENCE, TRIGLYCERIDES, HDL CHOLESTEROL AND GLUCOSE LEVELS WERE PREDICTOR VARIABLES.

	β	Standard error	Wald	df	p	Exp(B)
Systolic blood pressure	0.13	0.023	0.311	1	0.577	1.013
Diastolic blood pressure	0.006	0.027	0.053	1	0.817	1.006
Waist circumference	0.013	0.015	0.681	1	0.409	1.013
Triglycerides (mmol/L)	0.112	0.182	0.375	1	0.540	1.118
HDL -cholesterol (mmol/L)	2.271	0.655	12.023	1	0.001	9.693
Glucose (mmol/L)	0.694	0.257	7.288	1	0.007	2.002

bolic syndrome in patients with first episode MDD was 27.3%, whereas in patients with recurrent MDD it was 45.2%, independently of age and gender. Results indicate that long lasting depression and recurrence of depressive episodes significantly increase the risk of metabolic syndrome. Difference in the prevalence of the metabolic syndrome was present mainly due to differences in plasma glucose, triglycerides and HDL-cholesterol levels between analyzed groups.

According to previous studies, the prevalence of metabolic syndrome among patients with depression varies from 25 to more than 50%[5–13], which corresponds to the results of present study. The prevalence of metabolic syndrome in patients with first episode of MDD matches the lower limit, while the prevalence among patients with recurrent MDD coincides with the upper limit of a wide range of prior established prevalence.

To our knowledge, so far only one study took into consideration the duration of depression as a factor influencing the prevalence of metabolic changes later in life[14]. Gaysina and colleagues in a prospective study found that early onset of depression, in comparison with late onset, is a strong predictor of later obesity, but not of a completely developed metabolic syndrome. Moreover, that study did not take into account the recurring nature of depressive disorder and the appearance / absence of depressive episodes through the considered period of life. In our cross-sectional study, we found that completely developed metabolic syndrome is significantly more prevalent in patients with multiple depressive episodes and overall longer duration of depressive symptomatology. Taken together, it can be generally concluded that long lasting depression, compared with newly diagnosed first depressive episode, is associated with a higher rate of metabolic syndrome development.

Significantly higher prevalence of the metabolic syndrome among patients with recurrent MDD could be attributed to more common occurrence of depression-induced behavioral changes, such as sedentary lifestyle, overeating and general carelessness, which in turn require a longer period of time to entirely manifest their etiopathogenetic effects as completely developed metabolic syndrome[5,19].

Similarly, initiated pathophysiological mechanisms which overlap in both disorders, such as disturbed hypothalamic-pituitary axis activity, hypercytokinemia and dysregulated serotonergic neurotransmission[20–27], in patients with recurrent MDD »have enough time« to gradually, through a continuum of metabolic changes, finally result in a complete metabolic syndrome. Because this study did not include measurements of biological parameters associated with depressive disorder, such as plasma concentrations of serotonin, cortisol, proinflammatory cytokines and other inflammatory markers, further investigations are needed to elucidate which of them are related with a high prevalence of metabolic syndrome among depressed patients. Also, further research is necessary to determine whether there is any relation between the severity of depression and the metabolic syndrome occurrence.

Conclusion

This study provides the first evidence of a higher prevalence of metabolic syndrome among patients with recurrent MDD compared to patients with first episode MDD, pointing to the importance of the feature of recurrence and duration of depressive symptomatology in the etiopathogenesis of metabolic syndrome. The results suggest that metabolic syndrome in depressive patients could be considered as an extreme of a continuum of metabolic disturbances initiated with depression, probability of which increases with emergence of following depressive episodes. In this regard and in order to promptly initiate preventive measures for cardiovascular and cerebrovascular diseases it is very much advisable to multidisciplinary and systematically monitor depressive patients during their illness. Further studies are needed to elucidate if there is any relationship between the severity of depressive symptoms and prevalence of metabolic syndrome, as well as to determine the biological substrates of the present findings.

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R. Ljubičić

University of Zagreb, University Hospital Center »Sestre milosrdnice«, Department of Psychiatry, Vinogradska cesta 29, 10000 Zagreb, Croatia
e-mail: rudolf.ljubicic@yahoo.com

PREVALENCIJA METABOLIČKOG SINDROMA U DEPRESIVNIH BOLESNIKA – RAZLIKE IZMEĐU NOVODIJAGNOSTICIRANE PRVE EPIZODE I POVRATNE BOLESTI

SAŽETAK

Cilj ovog rada bio je utvrditi postoje li razlike u prevalenciji metaboličkog sindroma između depresivnih bolesnika s obzirom na trajanje depresivne simptomatologije (prva epizoda nasuprot povratnom poremećaju). U studiju je bilo uključeno ukupno 190 bolesnika s velikim depresivnim poremećajem dijagnosticiranim prema Međunarodnoj klasifikaciji bolesti, 10. revidirano izdanje (MKB 10)[1]. Ispitanici su bili podijeljeni u dvije skupine – skupinu bolesnika u kojih je dijagnosticirana prva epizoda velikog depresivnog poremećaja, te u skupinu bolesnika sa potvrđenom dijagnozom povratnog velikog depresivnog poremećaja. Metabolički sindrom je dijagnosticiran prema NCEP-ATP III kriterijima[2]. Rezultati su pokazali da je metabolički sindrom imao znatno veću prevalenciju među bolesnicima s povratnim depresivnim poremećajem (45,2%) no u bolesnika u kojih je dijagnosticirana prva epizoda povratnog depresivnog poremećaja (27,3%). Ove razlike bile su prisutne uglavnom zbog razlika u plazmatskim koncentracijama glukoze, triglicerida i HDL-kolesterola između ispitivanih skupina bolesnika. Rezultati studije upućuju na važnost trajanja depresivne simptomatologije te ponavljanja depresivnih epizoda kao čimbenika uključenih u etiopatogenezu pridruženog metaboličkog sindroma.