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**Vuksan-Ćusa, Bjanka; Marčinko, Darko; Nađ, Sanea; Jakovljević, Miro**

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## **Differences in cholesterol and metabolic syndrome between bipolar disorder men with and without suicide attempts**

Bjanka Vuksan-Ćusa\*, Darko Marčinko, Sanea Nađ, Miro Jakovljević

University Hospital Centre, Zagreb, Department of Psychiatry

General Hospital Virovitica , Department of Psychiatry

\*Corresponding author: Bjanka Vuksan-Ćusa, psychiatrist

Department of Psychiatry, University Hospital Centre Zagreb, Kišpatićeva 12, 10000 Zagreb

Tel. +385 1 2388 535; Fax. +385 1 2388 329

E-mail: [bjanka.vuksan@inet.hr](mailto:bjanka.vuksan@inet.hr)

### Abstract

Patient with mental illnesses such as schizophrenia and bipolar disorder have an increased prevalence of metabolic syndrome (MetS) and its components compared to general population. Among psychiatric disorders, bipolar disorder ranks highest in suicidality with a relative risk ratio of completed suicide of about 25 compared to the general population. Regarding the biological hypotheses of suicidality, low blood cholesterol level has been extensively explored, although results are still conflicting. The aim of this study was to investigate whether there were differences in the serum cholesterol levels in hospitalized bipolar disorder men patients with history of suicide attempts (N=20) and without suicide attempts (N=20). Additionally, we investigated if there were differences in the prevalence of MetS according to NCEP ATP-III criteria in these two groups of patients. Results of the study indicated significantly lower serum cholesterol levels ( $p=0.013$ ) and triglyceride levels ( $p=0.047$ ), in the bipolar disorder men with suicide attempts in comparison to bipolar disorder men without suicide attempts. The overall prevalence of MetS was 11/40 (27.5%). On this particular sample it was higher in the non-attempters 8/20 (40.0%) than in attempters 3/20 (15.0%) bipolar men group, but without statistical significance. Lower concentrations of serum cholesterol might be useful biological markers of suicidality in men with bipolar disorder.

## 1. Introduction:

Patient with mental illnesses such as schizophrenia and bipolar disorder have an increased prevalence of metabolic syndrome (MetS) and its components, risk factors for cardiovascular disease and type 2 diabetes (Ryan and Thakore, 2002; Newcomer, 2007 ) compared to general population in which incidence of MetS is also rising at an alarming rate (Nuggent, 2004). Although in the past years more attention has been devoted to the medical burden suffered by patients with schizophrenia, very recently similar concern have arisen for bipolar disorder patients. Previous studies on the prevalence of MetS in bipolar patients found 30% and 49% prevalence of MetS in US bipolar patients (Fagiolini et al., 2005; Cardenas et al., 2008), 32% prevalence of MetS in Turkish bipolar patients (Yumru et al., 2007) and 22.4% in Spanish bipolar patients (Garcia-Portilla et al., 2008). The etiology associated with this increased risk of MetS in bipolar disorder is unknown. In addition to psychosocial factors such as poverty , poor diet, lack of physical activities, increasing concern has focused on the association between second generation antipsychotics, weight gain and subsequent risk of hyperlipidaemia and diabetes. Patients with bipolar disorder have an additional risk for developing MetS because of hyperphagia and psychomotor retardation in atypical depression or comorbid conditions such as eating disorders, particularly within the bulimia/binge eating spectrum (McElroy et al., 2006).

Fagiolini et al. (2005) found that bipolar patients with MetS and patients endorsing the obesity criterion were more likely to report a lifetime history of suicide attempts.

Among psychiatric disorders, bipolar disorder ranks highest in suicidality with a relative risk ratio of completed suicide of about 25 compared to the general population (Baldessarini and Tondo, 2003). During their lifetime 80% of patients with bipolar disorder exhibit suicidal behaviour and 51% attempt suicide (Valtonen et al., 2005). Furthermore, suicide attempts in bipolar patients are more lethal as one in three attempts end up with completed suicide be compared to a ratio of 30:1 in the general population (Baldessarini et al., 2006). Compared with unipolar patients, suicide attempts in bipolar patients tend to be more lethal, particularly in males (Zalsman et al., 2006).

Suicidal behavior varied markedly between different phases of bipolar disorder and it is predominantly associated with depressive and mixed phases of the illness, rarely with pure manic phase. (Goldberg et al., 1999; Oquendo et al., 2000 ; Valtonen et al., 2007).

Among the biological hypotheses of suicidality, low blood cholesterol level has been extensively explored, although results are still conflicting. Numerous studies showed lower cholesterol levels in patients hospitalized after suicide attempt as compared to non attempters hospitalized patients (Sarchiapone et al., 2001; Guillem et al., 2002; Kim et al., 2002) with remained significant difference in men, but not in women, after gender stratification (Diaz-Sastre et al., 2007). On the other hand, there are some other studies showing no relationship between low cholesterol levels and suicide attempt (Roy et al., 2001; Tsai et al., 2002; Deisenhammer et al., 2004; Fiedorowicz et al., 2007) and even one recent study demonstrating higher cholesterol level in patients with suicide attempt in the past year (Brunner et al., 2006).

After several studies of our team regarding the role of low cholesterol in suicidal behavior in different psychiatric disorders (Marčinko et al., 2004, 2005, 2007a, 2007b, 2008), the current study was created to investigate if serum cholesterol level is decreased in male bipolar disorder patients with suicide attempts compared to non-attempters. Additionally, the aim of this study was to estimate if there were differences in the prevalence of metabolic syndrome between bipolar disorder male patients with and without lifetime suicide attempts.

## 2. Methods

### 2.1. Sample

Subjects were male patients (N=40) with bipolar disorder treated at the Department of Psychiatry, University Hospital Centre Zagreb during the period of 36 months. Within patients, 20 patients were consecutively admitted men with bipolar disorder with history of suicide attempt, and 20 patients were consecutively admitted men with bipolar disorder without history of suicide attempt. Needed sample size was calculated respected the following parameters: alpha error level of 95% ( $p < 0.05$ ), large effect size (Cohens  $d \geq 0.8$ ), infinite population, t-tests for two independent samples with homogenous variances). Needed sample size under this conditions were  $n=26$ . Due to the practical restraints (small number of patients that were free of medication during the last three months prior to the inclusion into the study) we accomplished somewhat smaller final sample ( $n=20$ ). The diagnosis of bipolar disorder was made according to diagnostic criteria of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), (WHO, 1996). According to ICD-10 criteria in suicide attempter group 7 patients were in depressive, 5 in manic and 8 in mixed episode. In non attempter group 6 patients were in depressive, 12 in manic and 2 in mixed episode.

Intensity of depressive symptoms was assessed by Hamilton Depression Rating Scale, HDRS-17 (Hamilton, 1960), while manic symptoms were assessed by Young Mania Rating Scale, YMRS (Young et al., 1978). Brief Psychiatric Rating Scale (BPRS-18) was used to estimate a broad range of psychopathology (Overall and Gorham, 1962). Clinical Global Impression severity, CGI sev (Guy, 1976) was performed to assess the severity of illness, and Suicide Assessment Scale, SUAS for symptoms of suicidality (Stanley et al., 1986). Suicide attempt, by definition, included intent to die, self-harm did not count. The trained psychiatrist performed clinical evaluation.

All participants were free of all psychotropic medication for the previous 3 months. Two groups of patients were closely matched for age. All subjects gave written consent for participation in the study after detailed information about the procedures. This study was approved by Clinical Hospital Center Medical Ethics Committee.

Only patients whose biochemical analyses from the time of admission were available were included in the study. Venous blood samples were collected within 24 h of admission. The exclusion criteria were: hypertension, diabetes mellitus, inherited disorders of lipoprotein metabolism, diagnosis of substance abuse, including alcoholism, eating disorder and organic brain syndrome.

## 2.2 Assessment

Venipuncture was performed for all subjects between 8 and 9 a.m. after 12 hours overnight fast. Immediately after collecting blood samples, serum concentration of total cholesterol, High density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides and serum glucose were determined using enzyme methods and commercial kits (Olympus Diagnostic, GmbH, Hamburg, Germany) on Olympus AU 600 automated analyzer. Inter-assay laboratory coefficients of variation were 3.2% for cholesterol, 2.5 for triglycerides and 3.0% for HDL-cholesterol. Reference intervals for the measured parameters were as follows: cholesterol <5.0 mmol/L, LDL <3.0 mmol/L, HDL >1.0 mmol/L, triglycerides <1.7 mmol/L and glucose >6,1 mmol/L.

In addition to biochemical parameters, height, weight, waist circumference and blood pressure were measured. Height and weight of each patient were recorded while they were standing barefoot in light clothes on the medical scale that measures height and weight. Body mass index (BMI) was calculated that body weight in kilograms was divided with squared height value in meters. Waist circumference, which is considered an accurate estimate of visceral adiposity, was measured at minimal respiration at high point of the iliac crest and at the level

of umbilicus. Sitting blood pressure was measured in subjects after they were interviewed in the sitting position for about 5 min while discussing neutral topics.

MetS was defined according to NCEP ATP III criteria (Expert panel JAMA, 2001). The presence of 3 or more of the following criteria was required to meet criteria for MetS:

1. abdominal obesity :waist circumference >102 cm in men and >88 in woman
2. hypertriglyceridemia : $\geq 1,7$  mmol/L
3. low HDL-cholesterol:<1,04 mmol/L in men and <1,29mmol/L in woman;
4. high blood pressure: $\geq 135/85$  mm Hg;
5. high fasting glucose: $\geq 6,1$  mmol/L

## 2.3 Data analysis

The results were expressed as mean values and standard deviations, 95% confidence intervals for means and medians. The differences in the socio-demographic variables between suicidal and non-suicidal groups were assessed using Chi square ( $\chi^2$ ) test or Fisher's exact test for 2x2 tables. We used one-sample Kolmogorov-Smirnov test to test the normality of distributions of continuous variables. Depending on the result of the K-S test, we used parametric t-test for variables with distributions close to normal (K-S  $p > 0.05$ ) and nonparametric Mann-Whitney U test for variables with non-normal distributions (K-S  $p < 0.05$ ) to compare two groups of patients.

Spearman correlation coefficient test was applied in searching relations between variables. In all tests, the criterion of significance was  $p < 0.05$ . Statistical processing of results was done by using commercial statistical package SPSS 11 (SPSS for Windows 11.0, SPSS, Chicago, IL, USA).

## 3. Results

Results of the study are presented in Table 1.

There were no statistically significant differences for age (M-W=176.5;  $p=0.529$ ), BMI (M-W=178.0;  $p=0.565$ ), waist (M-W=155.5;  $p=0.231$ ) and duration of illness (M-W=154.0;  $p=0.221$ ) values between bipolar male patients with and without suicide attempt.

We did not find significant differences between suicide attempters and non-attempters regarding different socioeconomic measures (work status, education, marital status and number of children) as well as for nicotine consumption ( $p > 0.05$ ). The BPRS scores did not differ significantly between bipolar suicide attempters and non attempters (M-W=186.5;  $p=0.718$ ), as well as CGI severity scores (M-W=198.5;  $p=0.968$ ).

HDRS scores were higher (M-W=144.0;  $p=0.134$ ) and YMRS scores were lower (M-W=139.5;  $p=0.102$ ) in suicide attempters group than in non attempters group, but without statistical significance. SUAS scores were significantly higher (M-W=116.0;  $p=0.023$ ) in attempters than in non attempters group.

Average total cholesterol was statistical significantly lower (M-W=109.0,  $p=0.013$ ) among suicide attempters (4.0+/-0.83) than among suicide non-attempters (5.1+/-1.58). The same was true in the case of triglycerides. Suicide attempters had statistically significantly lower (M-W=119.5,  $p=0.028$ ) triglycerides levels (1.4+/-0.52) than non-attempters (2.3+/-1.74).



Analysis showed that there are no statistically significant differences between bipolar patients with history of lifetime suicide attempts and bipolar patients without history of suicide attempts in HDL – cholesterol, LDL – cholesterol, blood pressure parameters and blood glucose levels ( $p>0.05$ ).

The overall prevalence of MetS in our sample was 27.5%. Among attempters group only 3 patients met the criteria for MetS and in the group of non-attempters 8 patients met the criteria for MetS. Although without statistical significance, the prevalence of MetS is higher in the group of patients who never made a suicide attempt ( $p=0.155$ ).

Suicidality measured by SUAS was significantly positively correlated with HDRS score (Spearman  $R=0.735$ ,  $p<0.001$ ), and significantly negatively correlated with YMRS score (Spearman  $R=-0.681$ ,  $p<0.001$ ).

Significant positive correlation was found for SUAS score and age (Spearman  $R=0.358$ ,  $p=0.023$ ), but no correlation was found for SUAS and duration of illness ( $p>0.05$ ).

We searched further for a possible correlation between SUAS score and anthropometric measures (BMI and waist) and did not find any significant correlation ( $p>0.05$ ).

## 4. Discussion

### 4.1. Principal findings

Results of the study showed differences between bipolar disorder male patients with and without suicide attempts both on biological and clinical level. Bipolar suicide attempters had statistically significantly lower levels of cholesterol and triglycerides compared to non attempters. LDL-C values were lower and HDL-C values were higher in attempters group, but without significance. These findings are in agreement with previous study results regarding low cholesterol and suicidal behavior in different psychiatric diagnostic categories (Sarchiapone et al., 2001; Bocchetta et al., 2001; Atmaca et al., 2002, 2007; Marčinko et al., 2004, 2005, 2007a, 2007b, 2008). Several different mechanisms have been suggested to explain the potential effect of low cholesterol levels on suicidality. Low cholesterol and suicidality might be related to decreased 5-HT transmission (Hawton et al., 1993) and reduced lipid micro–viscosity in the brain cell membrane surface, resulting in decreased 5-HT receptor function (Engelberg, 1992), inhibited 5-HT transmission, which may lead to a poorer suppression of impulsive behavior or to a depressive state.

In accordance with previous studies investigating depressive symptoms and suicidality in mood and/or psychotic disorders (Strakovski et al., 1996; Marčinko et al., 2008), our study also confirmed that suicidal patients had more pronounced depressive symptoms compared to

non-suicidal patients, which was evident in higher HDRS scores in suicidal patients and positive correlation between SUAS and HDRS scores.

The overall prevalence of MetS was 27.5% which is similar to the results of the previous studies investigating MetS in bipolar patients (Fagiollini et al., 2005; Yumru et al., 2007; Cardenas et al., 2008; Garcia-Portilla et al., 2008).

The relatively high prevalence of Met S (27.5%) is reason for concern because syndrome has very highly significant health implications, including a three to five fold increased risk of mortality due to coronary heart disease (Alexander and al., 2003; Bonora et al., 2004) and sixfold risk of developing type 2 diabetes (Laaksonen et al., 2002). On the other hand, results of our study showed that the prevalence of MetS was higher( on this particular sample, that is without reaching statistical significance) in non attempters bipolar disorder group compared to attempters group. We hypothesized that the serum lipid levels were responsible for the differences in the prevalence of MetS, since there were no significant differences in other modal subcomponents of MetS between bipolar attempters and non-attempters group. Contrasting results were shown in previous study (Fagiollini et al., 2005) demonstrating positive correlation between the presence of MetS, and obesity in particular, and a history of suicide attempts. The possible explanation for these differences may lie in different age and gender structure of the patient's sample. The metabolic syndrome (or at least some of its components, especially obesity) can contribute to a worse prognosis of bipolar disorder through its negative impact on general physical well-being and functioning, quality of life, self esteem and psychological well-being (Fagiollini et al., 2003). However, some other components of MetS regarding hyperlipidemia may possibly have positive impact on the course and outcome of the disease since low lipid levels are associated with increased suicidality.

To our knowledge, results of this study are the first to show relationship between reduced cholesterol, metabolic syndrome and suicidality in bipolar disorder. Since suicidality is complex behavior and influenced by biological markers and different psychological factors, recognizing the patients with biological predisposition to lack of behavioral control could be of help in prevention and treatment activities in routine clinical practice.

#### 4.2 Unanswered question and future research

Limitations of this study are small patient sample, patients in different phases of bipolar disorder and cross sectional design which reflects only a specific moment in time. Also, there was no information on patient's nutritive habits, lifestyle characteristics and daily physical

activities, as well as genetic factors, which may all contribute to the alterations in serum cholesterol and the presence of MetS in bipolar suicidal male patients.

#### 4.3. Conclusions

Our results suggest that bipolar disorder male patients with suicide attempt in history have lower levels of serum cholesterol and triglyceride as compared to those patients without suicide attempt. The overall prevalence of MetS in our bipolar patient population was 27.5%. The presence of MetS was associated with lower frequency of suicide attempts in history of male patient with bipolar disorder. These results implicate that serum lipid levels may have an important role in the neurobiology of suicide. Suicidality is a complex behavior influenced by many different biological and psychological parameters, so a better understanding of mutual relationships of these factors can facilitate more successful screening and treatment for suicidal patients.

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Table 1. Differences in demographic, biological and clinical parameters between bipolar disorder men with suicide attempts (N=20) and bipolar disorder men without suicide attempts (N=20)

Characteristics	Suicide attempters			Non attempters			U‡	P	Effect size (for significant results only)
	Mean±SD*	95% CI† for mean	Median	Mean±SD	95% CI for mean	Median			
Age(years)	36.4+/-9.95	31.69-41.01	32.0	36.7+/-14.43	29.94-43.46	29.5	176.5	0.529	-
Duration of illness /year/	10.6+/-7.01	7.27-13.83	9.5	8.8+/-7.05	5.45-12.05	5.5	154.0	0.221	-
BMI (kg/m <sup>2</sup> )	26.9+/-4.88	24.64-29.21	25.7	27.3+/-3.83	25.48-29.06	26.4	178.0	0.565	-
Waist circumference (cm)	94.1+/-12.14	88.42-99.78	92.5	97.3+/-9.22	92.94-101.56	96.5	155.5	0.231	-
Cholesterol (mmol/L)	4.0+/-0.83	3.6349-4.42	3.9	5.1+/-1.58	4.33-5.8	4.8	109.0	0.013	0.15
Triglycerides (mmol/L)	1.4+/-0.52	1.1749-1.66	1.3	2.3+/-1.74	1.44-3.06	1.6	119.5	0.028	0.10
LDL-c (mmol/L)	2.7+/-1.50	1.9982-3.40	2.3	3.1+/-1.32	2.46-3.7	3.0	157.5	0.253	-
HDL-c (mmol/L)	2.3+/-2.98	0.9498-3.74	1.2	2.1+/-2.67	0.83-3.33	1.2	197.0	0.947	-
GUK(mmol/L)	6.4+/-3.99	4.482-8.22	4.8	6.2+/-2.53	4.97-7.34	5.5	148.0	0.165	-
CGI severity	4.5+/-1.00	4.03-4.97	5.0	4.6+/-0.76	4.19-4.91	4.5	198.5	0.968	-
BPRS (score)	62.0+/-9.93	57.35-66.65	64.5	63.3+/-10.58	58.35-68.25	64.0	186.5	0.718	-
HDRS-17 (score)	24.6+/-10.29	19.78-29.42	26.5	19.4+/-10.5	14.49-24.31	15.5	144.0	0.134	-
YMRS (score)	17.7+/-15.67	10.32-24.98	14.0	26.8+/-17.25	18.73-34.87	33.0	139.5	0.102	-
SUAS (score)	54.9+/-6.83	51.65-58.05	55.5	47.7+/-9.96	42.99-52.31	50.5	116.0	0.023	0.16

\* Standard deviation

† 95% confidence interval

‡ Mann-Whitney U test with Exact statistical significance (P)