The lack of association between components of metabolic syndrome and treatment resistance in depression

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Abstract

Rationale Although a number of studies investigated the link between major depressive disorder (MDD) and metabolic syndrome (MetS), the association between MetS and treatment-resistant depression (TRD) is still not clear.

Objectives The aim of the study was to investigate the relationship between TRD and MetS and/or components of MetS and cardiovascular risk factors. Given the high prevalence of both conditions, the hypothesis was that TRD would be significantly associated with MetS.

Methods This cross-sectional study included 203 inpatients with MDD, assessed for the treatment-resistance, MetS and its components, and severity of MDD. Diagnoses and evaluations were made with SCID based on DSM-IV, National Cholesterol Education Program Adult Treatment Panel III criteria and the Hamilton Depression Rating Scale.

Results TRD prior to study entry was found in 26.1% of patients, while MetS was observed in 33.5% of patients. The prevalence of MetS did not differ significantly between TRD and non-TRD patients. In addition, the frequency of the altered values of particular components of the MetS or cardiovascular risk factors was not associated with treatment resistance in depressed patients. Patients with TRD were older, had higher number of lifetime episodes of depression and suicide attempts and longer duration of MDD compared to non-TRD patients.

Conclusions The occurrence of either MetS or the particular components of the MetS and other cardiovascular risk factors was similar between TRD and non-TRD patients. Although there is a bidirectional relationship between depression and MetS, neither MetS nor its components appear to influence treatment resistance to antidepressants.

Keywords Major depressive disorder (MDD) • Treatment-resistant depression (TRD) • Metabolic syndrome (MetS) • Components of the metabolic syndrome • Cardiovascular risk factors

Introduction

Major depressive disorder (MDD) is a complex and highly heterogeneous disorder with significant morbidity and mortality. In spite of growing number of different antidepressant drugs, treatment-resistant depression (TRD) remains an important public health issue, with an estimated 12-months prevalence of 2% in general population, for a stage 2 of treatment resistance (Nemeroff 2007). Treatment resistance has been related to a greater number of psychiatric hospitalizations (Shah et al. 2002), and higher medical costs compared to non-TRD patients (Gibson et al. 2010). Although TRD appears to be a common clinical condition, remarkably little is known about the underlying biology (Carney and Freedland 2009). Patients with TRD exhibit right superior, medio-frontal and striatal atrophy, as well as hippocampal and rostral anterior cingulate cortex changes, compared to non-TRD and healthy controls (Shah et al. 2002). Recent articles suggest differences in neural activity (Guo et al. 2012), and specific brain microstructural white matter abnormalities (Hoogenboom et al. 2012) in patients with TRD. Interestingly, the study which included TRD patients, revealed that those who were remitted at follow up had an increase in total brain volume, compared to non-remitters who showed decreased white-matter volume in the left anterior limb of the internal capsule (Phillips at al. 2012).

Only a few studies investigated clinical features associated with TRD, with inconsistent findings. Anxiety comorbidity, comorbid panic disorder and social phobia, personality disorder, suicidal risk, severity of symptoms, melancholic features, more than one hospitalization, recurrent episodes, early age at onset, and non-response to the first antidepressant received lifetime, were all associated with TRD (Souery et al. 2007). However, there is no reliable predictor of clinical response to antidepressants in general. Among many others, genetic factors, like genetic variations of serotonin transporter and P glycoprotein (MDR1) could play a role in the antidepressant response (Bozina et al. 2008; Mihaljevic Peles et al. 2008). Current on-going study performed by European Group for the Study of Resistant Depression (Schosser et al. 2012) has shown that response phenotype could be associated with genes variants of *catchol-O-methyltransferase* (*COMT*), *brain-derived neurotrophic factor* (*BDNF*) and serotonergic *5-HT2A* receptor, but not to cytochrome *P450*. Given the severe consequences of depression, better understanding of factors predicting response to antidepressants is needed.

Previous research suggested a bidirectional link between metabolic syndrome (MetS) and depression. In general, MetS may be an important predisposing factor for the later development of depression (Koponen et al. 2008), or cardiovascular disease (Pannier et al. 2006) in healthy subjects, while severe depressive symptoms or extremely stressful life event(s) may predict the risk for later development of the MetS (Raikkonen et al. 2007). Furthermore, depressed compared to

non-depressed subjects have greater risk of developing MetS, elevated waist circumference and increased glucose levels (Toker et al. 2008), while depression scores were significantly higher in healthy subjects with than without MetS (Pannier et al. 2006; Skilton et al. 2007; Toker et al. 2008).

Although a number of studies (Koponen et al. 2008; Pannier et al. 2006; Richter et al. 2010; Zeugmann et al. 2010) investigated the link between depression and MetS, and both MetS and treatment resistance are common in MDD patients, the association between MetS and TRD is still not clear (Chokka et al., 2006). The aim of our study was to determine whether MetS, or its components, or other cardiovascular risk factors, are related to treatment resistance in patients with MDD. The hypothesis of this study was that the frequency of MetS (or its components) would be higher in patients with TRD compared to non-TRD patients.

Methods

This cross-sectional study was conducted at University Hospital Center Zagreb, Department of Psychiatry, and University Clinics for Psychiatry Vrapce, Zagreb, Croatia, and included 203 inpatients, older than 18 years, hospitalized with the primary diagnosis of MDD. Patients were hospitalized according to the discretion of the attending physician, mostly due to severe depression which did not respond to the current treatment. In addition, some patients were hospitalized due to the suicidal risk. Clinical diagnosis of MDD on admission was further confirmed by the psychiatrists, using a SCID according to DSM-IV criteria (APA 1994). The severity of depression was evaluated using the 17 items Hamilton Depression Rating Scale (HDRS) (Hamilton 1960). The retrospective medical record review including previously diagnosed psychiatric and medical co-morbidities, and psychiatric and medical drug treatments, both current and prescribed during the previous 12 months, was also used. Demographic data, family, medical and psychiatric histories, and smoking habits, were recorded from the clinical interview with the patient and from medical records.

Treatment resistance prior to study entry was defined according to Souery et al. (1999) as a failure to achieve as a minimum 50% reduction from baseline scores on HDRS after no less than 2 courses of antidepressant monotherapy for at least 8 weeks (Little 2009), with full antidepressant dose (i.e. 20-40 mg/day for fluoxetine or its equivalent). Antidepressant drugs mostly prescribed were selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (NRIs), followed by tianeptine, mirtazapine, bupropion, reboxetine and maprotiline. Excluded were patients diagnosed with schizophrenia or schizoaffective disorder, bipolar disorder or organic mental disorder. We also excluded patients who had MDD with psychotic features and/or have received any mood stabilizers and/or antipsychotic drugs, in any dose, in previous 12 months. Patients who

received less than two antidepressant drug trials for the current depressive episode were also excluded.

Presence of MetS was diagnosed according to National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria (National Cholesterol Education Program (U.S.). Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. 2002). The criteria for MetS include at least three of the following: waist circumference ≥102 cm (men) or ≥ 88 cm (women); TG ≥ 1.7 mmol/L; HDL-C ≤ 1.00 mmol/L (men), ≤ 1.30 mmol/L (women); fasting glucose ≥ 6.1 mmol/L or use of medication for hyperglycemia and blood pressure ≥ 135/85 mmHg or use of medication for hypertension. All included patients gave a written informed consent after the procedure(s) were fully explained. The study protocol was approved by the local Ethics Committees.

Blood samples were taken as a part of routine hospital admission procedure, in the morning after an overnight fasting for 12 hours. Serum cholesterol, high density lipoprotein cholesterol (HDL) and TG levels were determined by the enzymatic color test for clinical analyzers, with the linearity within concentrations range of 0.64–18 mmol/L, 0.05-4.65 mmol/l and 0.11-11.40 mmol/l, respectively. Serum low density lipoprotein cholesterol (LDL) levels were determined by the enzymatic clearance assay, with linearity up to 22.4 mmol/L. Blood glucose was determined by the standard laboratory test. Waist circumference was measured using a non-stretch tape measure at the narrowest point between the lower costal (10th rib) border and the iliac crest. The body mass index (BMI) was calculated by dividing the weight (in kilograms) by squared height (in meters). Arterial blood pressure was measured in a sitting position using sphygmomanometer auscultatory method.

Statistical analysis

The results were expressed as means ± standard deviations (SD), number of cases, and adjusted odds ratios (OR) and 95% confidence intervals (CI). The differences between groups were evaluated using one-way analysis of variance (ANOVA). The multivariate logistic regression analysis was performed with TRD as dependent variable, several independent variables (high glucose, high TG, low HDL, high blood pressure, large waist circumference, MetS, high BMI, high cholesterol) and adjusted for age and sex. A χ^2 test was used to evaluate the frequency of depressed patients with or without TRD with present or absent MetS, and subdivided according to borderline value for the particular MetS components (elevated glucose, high TG and low HDL, increased blood pressure and waist circumference) and variables of cardiovascular risk (BMI, blood LDL and cholesterol levels, atherogenic index 1 and 2). Standardized residuals (R) were used to determine what categories were the major influence on the significant chi-square test statistic

(http://www.acastat.com/Statbook/chisqresid.htm), and were evaluated using Microsoft Excel. Due to multiple testing (Table 2), Bonferroni correction was used and the level of significance was set to $p \leq 0.0045$). The power (power) of calculation was set to be ≥ 0.800. A power calculation for large (eg: cohen's d=0.8) effect size for the MetS comparison between TRD and non-TRD groups was calculated using G*Power 3 program (Faul et al., 2007). In addition, we have also calculated the effect size (c) according to Cramer's c statistics (Daniel 1990). All results were evaluated using the statistical package Sigma Stat 3.5 (Jandell Scientific Corp. San Raphael, California, USA).

Results

The demographic data in patients with TRD and non-TRD are presented in Table 1. There were significant differences in age, number of depressive episodes, duration of illness and number of previous suicide attempts between patients with or without TRD (Table 1). TRD patients were significantly ($p = 0.001$) older, had significantly ($p = 0.002$) higher number of previous episodes of depression, significantly ($p = 0.001$) longer duration of MDD, and significantly higher number ($p = 0.005$) of suicide attempts than non-TRD patients (Table 1). The percentage of subjects in non-TRD group that had 0, 1, 2 or 3 suicide attempt(s) was 75.3, 16.7, 6.0 and 2.0%, respectively; while in TRD patients it was 47.2, 41.5, 9.4 and 1.9%, respectively. This difference in the frequency of the number of suicide attempts was slightly (but not significantly, after Bonferroni correction) different ($\chi^2 = 7.692$; $p = 0.0055$). To determine determine which category contributed to this difference, the absolute value of the residual (R) was calculated, and since R=2.78 (greater than 2.00) was detected in TRD patients with 1 suicide attempt, this frequency had a major influence on a marginally significant χ^2 test.

Overall 53 (26.1%) out of 203 patients had TRD at the study entry, while 33.5% of patients developed MetS (Table 2). MetS occurred in 31.3% of non-TRD patients and in 39.6% of patients with TRD, and this difference was not significant ($\chi^2 = 0.865$; $p = 0.352$). For the expected effect size of d=0.8; p=0.0045; power=0.800; df=1, the needed sample was calculated to be N=22 out of included 203 patients (Faul et al., 2007), so the study was well powered. However, with the expected sample size of d=0.8; p=0.0045; df=1, and total sample size N=203, to detect significant differences χ^2 should be 36.976 with a power=0.9999. According to Cramer's c statistics (Daniel 1990) the effect size (c) in the present study was very small (c=0.06). In addition, there was no significant ($p>0.0045$) difference in the frequency of patients with or without the presence of particular MetS components (elevated glucose, high TG and low HDL values, increased blood pressure and waist circumferences), or the values of the other variables of cardiovascular risk (BMI,

LDL, cholesterol levels, atherogenic index 1 and 2) between patients with and without TRD (Table 2).

Multivariate logistic regression analysis, adjusted for sex and age, with TRD set as a dependent variable, showed a non-significant trend (after Bonferroni correction) for the marginally higher ($p = 0.029$) glucose levels that predicted development of treatment resistance in patients with MDD. These patients had 2.39 times higher odds ratio (95% CI 1.090-5.245) to develop TRD (Table 3).

Discussion

The results of the present study showed that MetS occurred similarly in patients with or without TRD, and that distribution of patients with the presence of particular components of the MetS (elevated glucose, elevated TG, low HDL, elevated blood pressure and increased waist circumference), or alteration in other variables of cardiovascular risk (BMI, LDL, cholesterol, atherogenic index 1 and 2) did not differ significantly between patients with and without TRD. Marginally increased glucose levels were found more frequently in patients with TRD compared to non-TRD patients, but the significance was lost after Bonferroni correction.

In line with the other studies (Carney and Freedland 2009; Sourey et al. 2007) treatment resistance was present in approximately one third of our patients with MDD. Patients with TRD were older, had longer duration of disease, higher number of both depressive episodes and suicide attempts, as well as increased current suicidality, compared to non TRD patients. MetS was observed in 33.5% of patients which is agreement with the 24-36% prevalence of MetS in patients with depression (Koponen et al. 2008; Pannier et al. 2006). To the best of our knowledge, this is the first study investigating the association between TRD, MetS and its components. Although both TRD and MetS appear with high frequency in patients with MDD, our results did not show that MetS occurs more frequently in patients with TRD.

There are several factors that should be discussed. In general, our sample was characterized by patients with relatively late age of onset of MDD (both TRD and non-TRD patients experienced their first episode after the age of 40 years). Given that patients with TRD were older, vascular etiology could also have contributed to MDD onset and the development of treatment resistance. Preclinical vascular disease (Muldoon et al. 2007) was associated with blunted central serotonergic function, measured by prolactin response to citalopram in healthy volunteers (Muldoon et al. 2006). Altered serotonergic function, such as decreased post-synaptic 5-HT-2A receptors in the dorsal regions of the prefrontal and the anterior cingulate cortex, were observed in antidepressant-free TRD patients (Baeken et al. 2012). However, the results of the present study show no differences

between patients with and without TRD in the frequency of components of MetS, BMI and both atherogenic index 1 and 2. Those findings strongly argue against the differences in vascular pathology between patients with and without TRD.

Few studies investigated the association between lipid levels and antidepressant response. In one study (Papakostas et al. 2003) a higher TG level was found in patients with TRD compared to non-TRD patients. Elevated cholesterol levels were associated with poor treatment response to noradrenergic antidepressants in TRD patients (Papakostas et al. 2003). A poor treatment response and high cholesterol levels were also observed in patients with MDD treated with SSRI fluoxetine (Iosifescu et al. 2005) or paroxetine (Muck-Seler et al. 2011). Moreover, non-responders to paroxetine had increased baseline cholesterol, LDL, TG levels and the LDL/HDL ratio compared to responders to paroxetine (Muck-Seler et al. 2011). The discrepancies with our findings could be due to different methodological issues. In contrast to the inclusion criteria in the present study, our earlier study (Muck-Seler et al. 2011) included patients who were drug-free, non-suicidal, had no diabetes and did not receive cholesterol-lowering drugs. Furthermore, patients in the previous studies (Iosifescu et al. 2005; Muck-Seler et al. 2011) were younger compared to patients included in the present study, suggesting that increased cholesterol levels might influence poor response at least to SSRIs, predominantly in younger patients. The influence of age on response to non-pharmacological treatment of depression was also reported. Patients at age<60 years had greater response to repetitive transcranial magnetic stimulation compared to older patients (Pallanti et al. 2012). On the other hand, our results are in line with data from Amital et al. (2012), who found no difference between TRD and non-TRD patients in the prevalence of comorbid somatic disorders, including diabetes, hypertension and ischemic heart disease. Although the prevalence of MetS increases with age, it is possible that factors other than MetS, influence poorer response to antidepressants in older age.

Suicidal behaviour is a complex clinical syndrome, related to numerous biological, sociological and psychological factors (Olin et al. 2012). We have found that TRD was associated with current suicidality and that TRD patients more frequently had at least one prior suicide attempt, which suggest more frequent suicidal behaviour in TRD study population. So far, only one study (Papakostas et al. 2003) investigated the suicidality in TRD and found that more than half of patients with TRD reported thoughts or wishes of death. The higher number of previous suicide attempts in our TRD compared to non-TRD patients is in line with the results of Amital et al. (2008). In spite of the increased suicidality, our patients with TRD and non-TRD had similar severity of depression. This is in contrast with more severe symptoms of depression observed in

patients with TRD (Amital et al. 2008) that were treated not only with antidepressant, like in the present study, but with combination of antidepressants and antipsychotics.

Limitations of the study are cross-sectional design and the fact that patients were treated with different antidepressants. Antidepressant drug concentration was not determined, and compliance with the antidepressant regimen was not checked. The information about childhood exposure to trauma was not available. Since the sample was cross-sectional and included depressed inpatients, this sample is not generalizable to the whole community sample. This study had adequate power (≥0.800) to detect significant differences in age, number of depressive episodes, duration of illness and number of previous suicide attempts between patients with or without TRD. At the study entry we had adequate number of patients, N=203 out of needed N= 22, expecting a high effect size. However, the number of patients included in the study was less than adequate for the small effect size (c=0.06) detected in our study, since a similar frequency of MetS was detected between patients with or without TRD. In addition, less than adequate power was found in the frequency of patients with or without presence of components of MetS or other variables of cardiovascular risk between patients with and without TRD, as stated in the results, suggesting that these results should be considered preliminary, and might have been significant if sufficient sample size was available. Therefore, further research is needed on a larger number of patients with TRD.

Conclusions

The results of the study did not confirm the hypothesis that MetS, its components or variables of cardiovascular risk factors would be found more frequently in patients with TRD compared to non-TRD patients. Although methodological and sample size limitations do not allow definitive conclusions, and given the long-term health consequences of both MetS and TRD, the relationship between components of MetS and TRD deserves further investigation in adequately powered studies.

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Table 1. The demographic and clinical variables in patients with treatment resistant depression (TRD) and without TRD (non-TRD). Results are expressed as mean ± SD. The number of subjects is given in brackets.

	Patients with MDD (203)			
	Non-TRD (150)	TRD (53)	One-way ANOVA df=1, 201	
			F	P
Age (years)	49.3 ± 9.7	57.2 ±10.3	25.572	0.001
Number of episodes	2.9 ± 1.9	3.9 ±1.7	10.209	0.002
Duration of disease (years)	6.4 ± 4.9	9.3 ± 6.2	11.132	0.001
Total HDRS scores	26.1 ± 5.9	27.7 ± 6.3	2.608	0.108
Number of suicidal attempts	0.35 ± 0.69	0.66 ± 0.73	7.916	0.005
Current suicidality (HDRS item 3 scores)	1.14 ± 1.12	1.51 ± 1.28	3.960	0.048

Table 2. The number of patients with treatment resistant depression (TRD) and without TRD (non-TRD) with the presence of altered variables of metabolic syndrome (glucose, triglycerides levels, HDL levels, blood pressure and waist circumference) and variables of cardiovascular risk (BMI, LDL and cholesterol levels; atherogenic index 1 an d 2). N is the number of patients.

	Patients with MDD (203)		
	Non-TRD (150)	TRD (53)	
Glucose			
< 6.1 mmol/l	111	32	$\chi^2 = 2.867$; df=1; p=0.090
≥ 6.1 mmol/l	39	21	
HDL			
>1.3 mmol/l women; > 1.0 mmol/l men	115	40	$\chi^2 = 0.115$; df=1; p=0.735
≤ 1.3 mmol/l women; ≤ 1.0 mmol/l men	35	13	
Triglycerides			
< 1.7 mmol/l	58	25	$\chi^2 = 0.846$; df=1; p=0.358
≥ 1.7 mmol/l	92	18	
Blood pressure			
< 135/85 mm Hg	88	27	$\chi^2 = 0.663$; df=1; p=0.119
≥ 135/85 mmHg	62	26	
Waist circumference			
< 88 cm women; < 102 cm men	103	33	$\chi^2 = 0.465$; df=1; p=0.495
≥ 88 cm women; ≥ 102 cm men	47	20	
Metabolic syndrom			
No	103	32	$\chi^2 = 0.865$; df=1; p=0.142
Yes	47	21	
BMI			
< 27.50 kg/m^2	79	29	$\chi^2 = 0.009$; df=1; p=0.923
≥ 27.50 kg/m^2	71	24	
Cholesterol			
< 5.2 mmol/l	92	24	$\chi^2 = 0.464$; df=1; p=0.496
≥ 5.2 mmol/l	53	29	
LDL			
< 3.0 mmol/l	57	28	$\chi^2 = 2.956$; df=1; p=0.086
≥ 3.0 mmol/l	93	25	
Atherogenic index 1 (Cholesterol/LDL ratio)			
< 4.0 women; < 5.2 men	122	49	$\chi^2 = 2.857.$; df=1; p=0.091
≥ 4.0 women; ≥ 5.2 men	28	4	
Atherogenic index 2 (LDL/HDL ratio)			
< 2.3 women; < 3.0men	90	36	$\chi^2 = 0735.$; df=1; p=0.391
≥ 2.3 women; ≥ 3.0 men	60	17	

Table 3. Multivariate logistic regression analysis in patients with MDD with TRD as dependent variable adjasted for age and sex.

Patients with MDD			
	Odds ratio	95% CI	p
High glucose levels (mmol/l)	2.391	1.090-5.245	0.029
High TG levels (mmol/l)	0.768	0.374-1.579	0.473
Low HDL (mmol/l)	1.002	0.444-2.262	0.997
High blood pressure (mmHg)	1.231	0.566-2.675	0.6
Large waist circumferences (cm)	0.983	0.466-2.072	0.963
Metabolic syndrome	1.282	0.606-2.710	0.516
High BMI (kg/m2)	0.935	0.419-2.089	0.871
High cholesterol (mmol/l)	0.539	2.601-1.114	0.095