

# Metabolic Syndrome and C-Reactive Protein in Patients with Depressive Disorder on Antidepressive Medication

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## SUMMARY

**Introduction** Recurrent depression is a psychiatric disorder of which etiology and pathogenesis might be related to immune response. Metabolic Syndrome (MetS) and its components are also strongly associated with elevated inflammatory indicators, as so as the body mass index (BMI) and total cholesterol levels.

**Objective** Objective of this study was to investigate if there was any difference in C-reactive protein (CRP) levels in patients with recurrent depressive disorder, treated with antidepressants, compared to a healthy control group of subjects and if there was an association between increased CRP levels and the presence of MetS in these two groups.

**Methods** Sixty subjects entered the study; of these 35 patients with the diagnosis of recurrent depressive disorder, while the healthy control group included 25 subjects. MetS was defined according to the NCEP ATP III criteria. The cut-off point for CRP was set at >5 mg /L.

**Results** There was no statistically significant difference in the prevalence of MetS and CRP values between the studied groups. Waist circumference and total cholesterol levels were significantly higher in the experimental group. Patients that fulfilled the criteria for MetS showed significantly higher values of central obesity and arterial hypertension in the experimental group as well. The elevated CRP levels were associated with increased frequency of MetS in depressed patients.

**Conclusion** Both CRP levels and metabolic risk profile screening, according to the international criteria, may be beneficial in order to obtain better assessment for depressive long term medicated patients.

**Keywords:** C-reactive protein; Metabolic Syndrome; depression; SSRI pharmacotherapy

## INTRODUCTION

Infectious and inflammatory processes could potentially play an important role in the etiology and pathogenesis of depressive disorder [1, 2]. C-reactive protein (CRP) is one of positive acute phase proteins that is synthesized in the liver and then excreted in the blood. Increased CRP levels are associated not only with acute but with chronic infections too [3].

Depression has been shown to be associated with activation of the inflammatory response. These changes include increased numbers of peripheral leucocytes, both monocytes and neutrophils [4]. This acute-phase response is an integral part of the inflammatory response and its purpose is to enable protein mobilization, which serves to limit tissue damage and stimulate repair. CRP may be useful in predicting cardiovascular events in patients with coronary heart disease [5]. When traditional risk factors for coronary heart disease are adjusted, depressed individuals have a risk double that of the non-depressed population [6].

Newcomer [3] defined the Metabolic Syndrome (MetS) as a chronic mild inflammatory state. Furthermore, the presence of MetS is most important predictor of premature onset

of cardiovascular disease (CVD). CRP, as the most specific biomarker of inflammation, is the independent risk factor for CVD as well. The Amsterdam Longitudinal Ageing Study reported a relative risk of cardiac mortality of 1.6 associated with depressive symptoms. However, this cardiac mortality relative risk increased to 3.8 for those who were clinically depressed [7]. Laboratory and epidemiological data showed that CRP is associated mostly with insulin resistance and obesity, but also with other sub-components of MetS [8]. The link between depression and coronary heart disease may be mediated through inflammation. Atherosclerosis is preceded by inflammation with increased production of acute-phase proteins, including CRP and pro-inflammatory cytokines [9]. It seems reasonable to assume that depression increases the risk of coronary heart disease through its pro-inflammatory biology [10].

## OBJECTIVE

Aim of this study was to investigate if there are any differences in parameters that constitute MetS, as well as in CRP levels, total cholesterol, and body mass index (BMI) in patients with re-

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current depressive disorder treated with selective serotonin reuptake inhibitor (SSRI) medication, compared to healthy controls. Further, we wanted to examine variables – predictors of MetS in both study groups. For the experimental group of patients the authors' interest was to determine if variables such as severity of depression measured by HAMD-21 scale [11], length of SSRI therapy, length of illness duration and smoking habits have an impact on CRP values >5 mg/L.

## METHODS

Sixty subjects entered the study; 35 of them were patients with recurrent depression disorder on SSRI antidepressant medication in the Daily Hospital Ward of the Special Mental Hospital "Gornja Toponica", Niš, and 25 healthy control subjects. The diagnosis of recurrent depressive disorder was made according to the diagnostic criteria of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10: F33) [12]. We used the Hamilton Depression Rating Scale (HAMD-21) for depression symptoms severity for the patients from the experimental group. A written informed consent was obtained from all participants, under procedures approved by the Local Ethics Committee and in accordance with the Helsinki Declaration. 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. CRP serum levels were determined using immunoturbidimetric method. The cut-off point for CRP elevation was set at 5 mg/L.

MetS was defined according to the Third Report of the Adult Treatment Panel – National Cholesterol Education Program (NCEP ATP III) criteria [13]; any 3 of 5 Categorical Cut-points: 1. Central adiposity (elevated waist circumference; 102 cm in men, 88 cm in women); 2. Elevated triglycerides >1.7 mmol/L, or on drug treatment for elevated triglycerides; 3. Reduced HDL-C <1.0 mmol/L in men, <1.3 mmol/L in women, or on drug treatment for reduced HDL-C; 4. Elevated blood pressure >130 mm Hg systolic blood pressure or >85 mm Hg diastolic blood pressure or on antihypertensive drug treatment in patients with history of hypertension; 5. Elevated fasting glucose >5.6 mmol/L or on drug treatment for elevated glucose.

BMI was calculated by measuring patients' weight and height (kg/m<sup>2</sup>). Waist circumference (marker of central adiposity) was measured in the midpoint of distance between the costal arc and iliac crest when the patient was standing up and in midexpirium. Blood pressure was measured with an aneroid sphygmomanometer in the office setting.

The subjects excluded from the study were those who showed symptoms of chronic or acute infection, allergies, past history of autoimmune diseases, or any other condi-

tion known to have affected the immune system for at least 2 weeks before investigation. They were also free of using other concomitant drugs known to alter immune function.

Statistical analyses: baseline characteristics were compared by the t-test for independent samples. For categorical variables the chi-square test was used. Univariate logistic regression analysis was used to assess predictors of MetS and high values of CRP, respectively. The analyses were done using SPSS for Windows Version 18.0. Probability level of  $p < 0.05$  was considered to be statistically significant.

## RESULTS

Experimental group of patients (diagnosis of recurrent depression disorder) included 35 subjects (18 male, 17 female) of average age  $47.85 \pm 7.35$  years. The average age of the healthy control subjects ( $n=25$ ) was  $45.08 \pm 4.93$  years.

All subjects from the experimental group were on the permanent antidepressant SSRI medication from three months up to 24 months duration (mean value  $8.57 \pm 5.46$  months). Severity of depressive symptoms measured by HAMD-21 scale showed that the majority of experimental group of patients were euthymic ( $n=19$  or 54.29%), with HAMD score 8 or less, and the rest had mild depression ( $n=16$  or 45.71%), with HAMD scores range 17-24. The average duration of illness (diagnosis of recurrent depressive disorder according to ICD 10 criteria) was  $7.86 \pm 5.13$  years.

Table 1 shows demographic, biochemical and inflammatory values in these two groups. Statistically significant differences ( $p < 0.001$ ) were found for variables waist circumference and total cholesterol levels.

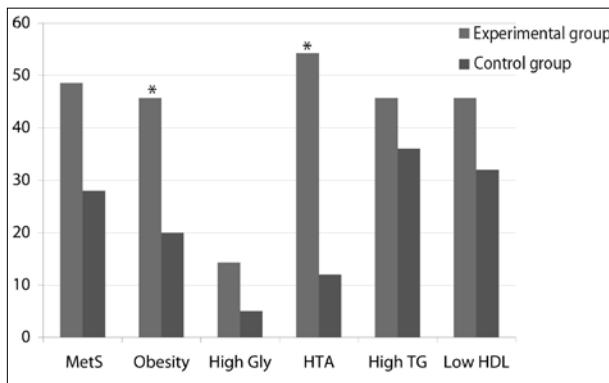
Graph 1 shows the prevalence of patients with MetS in the experimental and control group, according to the presence of NCEP ATP III criteria and its individual components. The prevalence of MetS was 48.6% in the experimental group, compared to 28% in the control group ( $\chi^2=2.53$ ;  $p=0.112$ ), with no statistically significant difference. However, two out of five constituting parameters of

**Table 1.** Demographic features, biochemical and inflammatory variables of the study groups

Variable	Experimental group (n=35)		Control group (n=25)		p value
	$\bar{X}$	SD	$\bar{X}$	SD	
Gender (male/female)	18/17		13/12		0.586
Age (years)	47.85	7.35	45.08	4.93	0.197
BMI (kg/m <sup>2</sup> )	26.63	4.05	25.43	2.77	0.207
Waist (cm)	96.57	10.06	85.68	13.68	0.001*
Chol (mmol/L)	5.38	0.94	4.36	0.52	0.001*
Tg (mmol/L)	1.72	0.85	1.57	0.39	0.412
LDL-C (mmol/L)	3.01	0.94	2.95	0.37	0.750
HDL-C (mmol/L)	1.20	0.26	1.24	0.22	0.545
CRP (mg/L)	4.72	2.91	4.90	1.34	0.781
Gly (mmol/L)	4.71	1.94	4.36	0.43	0.374

\* statistically significant p value

n – number of patients; X – mean value; SD – standard deviation; BMI – Body Mass Index; Waist – waist circumference; Chol – total cholesterol; Tg – triglycerides; LDL-C – LDL cholesterol; HDL-C – HDL cholesterol; CRP – C-reactive protein; Gly – fasting glucose



**Graph 1.** Prevalence (%) of metabolic syndrome and its individual components in the experimental and control group. Distribution of patients according to the NCEP ATP III criteria [13]

\* statistically significant difference

MetS – metabolic syndrome; Obesity – central adiposity; High Gly – high fasting glucose; HTA – arterial hypertension; High TG – high triglycerides; Low HDL – low high density lipoprotein

**Table 2.** Odds ratio (OR), significance (p) and confidence interval (CI) for Metabolic Syndrome correlates in the experimental group (n=35)

Factor		OR	95%CI	p
Smoking	[No]	/	/	/
	Yes	0.716	0.187–2.744	0.626
CRP		4.688	1.540–14.269	0.007*
BMI		1.211	0.974–1.505	0.085
SSRI length		0.984	0.863–1.122	0.812
HAMD score		0.988	0.815–1.197	0.900

\* statistically significant p value

[/] – referent group; SSRI length – length of permanent SSRI medication (months)

**Table 3.** Odds ratio (OR), significance (p) and confidence interval (CI) for Metabolic Syndrome correlates in the control group (n=25)

Factor		OR	95%CI	p
Smoking	[No]	/	/	/
	Yes	9.429	0.927–95.886	0.058
CRP		6.042	1.089–33.518	0.040*
BMI		2.472	1.216–5.028	0.012*

\* statistically significant p value

[/] – referent group

**Table 4.** Odds ratio (OR), significance (p) and confidence interval (CI) for the correlates of high CRP values (>5 mg/L) in experimental group (n=35)

Factor		OR	95%CI	p
Smoking	[No]			
	Yes	4.156	1.399–12.347	0.010*
Illness length (years)		0.964	0.842–1.104	0.597
SSRI length (months)		1.070	0.940–1.217	0.305
Mild depression		1.069	0.279–4.099	0.902

\* statistically significant p value

[/] – referent group; mild depression – patients with HAMD score 8–17 (n=16)

MetS – obesity (i.e. central adiposity, high waist circumference):  $\chi^2=4.17$ ;  $p=0.04$ , and arterial hypertension:  $\chi^2=11.04$ ;  $p<0.001$  – showed statistical significance between the study groups, in favor of the experimental group of patients.

The authors wanted to investigate which were the most important correlates of MetS. For the experimental group of patients, results are presented on Table 2. Univariate logistic regression pointed to CRP as a statistically signifi-

cant variable (OR=4.668; 95%CI=1.540–14.269;  $p=0.007$ ). Neither HAMD scores, length of antidepressants therapy, nor BMI values were found as significantly different.

In the control group the same method pointed at both CRP (OR=6.042; 95%CI=1.089–33.518;  $p=0.04$ ) and BMI (OR=2.472; 95%CI=1.216–5.028;  $p=0.012$ ) as significant correlates of MetS (Table 3).

Variables such as the length of SSRI medication (months), length of depression illness (years), or severity of symptoms (patients with mild depression according to HAMD in our sample) were not significant indicators of high CRP values in the experimental group of patients. Derived data using the univariate logistic regression pointed at smoking habit only as a statistically significant correlate of high CRP values >5 mg/L (OR=4,156; 95%CI=1.399–12.347;  $p=0,01$ ) (Table 4).

## DISCUSSION

The prevalence of MetS in our experimental group of patients with depression disorder was 48.6%, compared to 28% in the healthy control group of patients ( $p=0.11$ ). Among the US adults 24% have MetS, and the prevalence increases with age (44% at age 60 years) [14]. The prevalence of MetS, according to the NCEP criteria, has been recently assessed in two independent investigations of patients with bipolar disorder. The first study evaluated 171 patients and found the MetS prevalence of 30% [15]. The other study reported the MetS prevalence rate of 32% in a group of 125 bipolar patients [16]. Moreover, MetS was reported in 42.4% of 33 patients with schizoaffective disorder, bipolar type [17]. Similar to these results, a relatively high percentage of MetS in our experimental group of patients should be considered in relation of their average age ( $47.85\pm 7.35$  years) as well as the average illness duration ( $7.86\pm 5.13$  years) and the presumption of poor physical activities.

Measured demographic (age, gender), physical (body mass index, waist circumference) biochemical (total cholesterol, LDL-C, HDL-C, fasting glucose, triglycerides) and inflammatory (CRP) parameters showed a statistically significant differences ( $p<0.001$ ) between the two study groups only for waist circumference and total cholesterol levels, favoring the experimental group of patients. Among the patients who fulfilled the criteria for MetS, statistically significant differences between the study groups were demonstrated for central obesity (high waist circumference) and arterial hypertension (elevated blood pressure or on antihypertensive drug treatment). Two groups were compared with respect to lipid profiles of the cases in the study of Kirilmaz et al. [18]. Statistically significant elevations in levels of total cholesterol, triglycerides, blood pressure and LDL-C and a significantly decreased level of HDL-C were detected in the patients with MetS compared with the control group. According to body fat distribution, any increase in the mass of abdominal fat is an important determinant of mortality and morbidity and is in relation to many cardiovascular risk factors.

As the most important correlate for MetS presence in our experimental group of patients, univariate logistic regression indicated only CRP value at a statistically significant level. Neither HAMD scores, length of antidepressants therapy, nor BMI values were found to differ. In the control group, the same method pointed at both CRP and BMI as significant correlates of MetS. Numerous studies [19, 20] have now confirmed that CRP levels are elevated in patients with MetS. It has been claimed that there is a chronic and low-degree inflammatory status in MetS. CRP indicates the existence and degree of inflammation involving the vascular endothelium. Yet, it is still controversial as to whether CRP is an inflammatory parameter or a risk factor. There is a linear relationship between the number of metabolic features and increasing levels of CRP. Furthermore, Festa et al. [21] in the Insulin Resistance and Atherosclerosis Study (IRAS) showed that CRP was positively correlated with BMI, waist circumference, triglycerides, cholesterol, LDL-C, plasma glucose, and fasting insulin, and inversely correlated with HDL-C. The strongest associations are observed between CRP levels, central adiposity, and insulin resistance. The largest study to-date that examined the association between inflammation and MetS was the NHANES III study [22] which reported that CRP and fibrinogen levels and leukocyte counts were significantly high in patients with MetS.

The cut-point for elevated values of CRP in our study was 5 mg/L. The authors also explored relationship among high CRP values and variables such as severity of depression measured by HAMD scale, length of SSRI therapy, length of illness duration and smoking habits. In our experimental group, we had a subgroup of 16 patients qualified as „mild depression“ according to the HAMD score. This level of severity of depressive symptoms was not found as a correlate of elevated CRP values, neither did the length of antidepressive medication nor the length of the illness. However, some authors found an association of increased CRP levels with the severity of depressive symptoms [23] and normalization after antidepressant treatment [24], but findings are not consistent across studies. The reasons why CRP is selectively altered in manic, but not in depressed or euthymic patients are unknown [18]. The limitation of this study was that all patients who entered the study were taking SSRI medication for a certain time. Several studies have previously examined the association between CRP and depression, and the preponderance of evidence supports the conclusion that depression is associated with

CRP but is confounded or mediated by other variables, particularly those that reflect fat mass [25, 26]. In a small case-control study in 1996, Sluzewska et al. [27] showed that CRP levels were significantly higher in patients with major depression compared with normal controls. No adjustment for possible confounders was performed.

Smoking habit was significant predictor for high CRP values in our study group of patients with recurrent depressive disorder, while other examined variables (length of SSRI medication, length of depression illness, severity of depressive symptoms) were not. Similar observations reported Douglas et al. [28], on the large group of 696 depressed patients, where total depression score did not independently correlate with CRP, and that any correlation between depression score and CRP could be explained by a relationship with other variables, such BMI, smoking habit, and blood pressure.

## CONCLUSION

There was no statistically significant difference in the prevalence of MetS and CRP values between the experimental group of patients suffering from recurrent depression disorder treated with antidepressants and healthy control subjects. Waist circumference and total cholesterol levels were significantly different in favor of the experimental group.

Elevated CRP levels were associated with increased risk for the development of MetS in depressed patients, while both CRP values and BMI were significant correlates of MetS for the control group. Smoking habit was a considerable predictor for high CRP values (5 mg/L) in the experimental group of patients.

The severity of depression symptom (measured by HAMD score) and length of illness, indicated by the length of antidepressant drug treatment, did not show significant correlation with MetS and CRP.

Unfortunately, the scarcity of patients, the absence of subgroup of severely depressed patients (without previous medication) were a relevant limitation of our study.

Inflammation plays an important role in atherosclerotic complications, which is activated in MetS. Increased number of MetS components is strongly associated with elevated inflammatory and metabolic markers. Measurement of serum inflammatory parameters in psychiatric patients with MetS may be beneficial in prediction, detection and management of cardiovascular events.

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## Метаболички синдром и C-реактивни протеин код болесника са депресивним поремећајем који примају антидепресивну терапију

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### КРАТАК САДРЖАЈ

**Увод** Рекурентни депресивни поремећај је психијатријски ентитет чија су етиологија и патогенеза у вези с имунским одговором. Метаболички синдром са својим компонентама такође је у уској вези с повишеним вредностима показатеља запаљења, индексом телесне масе и вредностима укупног холестерола у серуму.

**Циљ рада** Циљ студије био је да истражи има ли разлике у нивоима C-реактивног протеина (CRP) између испитаника са дијагностикованим рекурентним депресивним поремећајем који примају антидепресивну терапију (експериментална група) и здравих испитаника (контролна група), као и да ли постоји веза између повећаних нивоа CRP и заступљености метаболичког синдрома у ове две групе испитаника.

**Методе рада** Студијом је обухваћено 60 испитаника: 35 са дијагнозом рекурентног депресивног поремећаја и 25 здравих особа. Метаболички синдром је дефинисан према критеријумима NCEP ATP III. Повећаним вредностима CRP сматрале су се оне веће од 5 mg/l.

**Резултати** Није утврђена статистички значајна разлика у преваленцији метаболичког синдрома и нивоа CRP између испитиваних група. Обим струка и ниво укупног холестерола били су статистички значајно већи у експерименталној групи. Код испитаника који су задовољили критеријуме за метаболички синдром уочена је статистички значајна разлика у његовим конститутивним параметрима „централна гојазност“ и „артеријска хипертензија“, такође у корист експерименталне групе. Повећани нивои CRP у серуму били су удружени с повећаним ризиком од постојања метаболичког синдрома у групи депресивних испитаника.

**Закључак** Мерење нивоа CRP у серуму и утврђивање постојања метаболичког синдрома према међународним критеријумима могу бити врло корисни у обезбеђивању квалитетнијег лечења депресивних болесника на дужевременској медикацији антидепресивима.

**Кључне речи:** C-реактивни протеин (CRP); метаболички синдром; депресија; SSRI фармакотерапија