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CONNECTION BETWEEN INFLAMMATORY MARKERS, ANTIDEPRESSANTS AND DEPRESSION

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SUMMARY – The aim of this study was to explore the role of inflammatory markers in the occurrence of depression. The concentrations of inflammatory markers were analyzed in the groups of healthy subjects and subjects with major depressive disorder (MDD) initially and after one-month antidepressant therapy in the latter. The intention was to demonstrate the role of inflammatory markers in the development of MDD by differences in their concentrations and to explain the mechanism of depression development. This would help us expand our understanding of the occurrence of depression and enable introduction of some new methods in the treatment and diagnosis of depression. Study results showed a statistically significant difference in the concentrations of inflammatory markers (C-reactive protein (CRP), interleukin-6 and tumor necrosis factor alpha) between the group of MDD subjects and control group of healthy subjects. These concentrations were higher in MDD subjects. A statistically significant difference was also found in CRP concentration before and after antidepressant therapy administered to MDD patients, i.e. it was lower after antidepressant therapy. Study results pointed to the efficacy of antidepressant therapy for depression by reducing the concentration of this inflammatory marker.

Key words: *Depression; Cytokines; Mechanism of antidepressant action*

Introduction

Integrative approach is the only currently possible and accepted in studying the etiology of major depressive disorder[1]. Through integrative approach, i.e. interaction of the genetic, other biological and psychosocial factors, their joint influence in major depression has been recognized[2]. Growing evidence shows that immune modulators may play an important role in the pathophysiology of mood disorders or cause specific mood symptoms[3-5]. The immune system and the central nervous system create a two-way communication network[6], and evidence for correlation between the immune system and mood disorders comes from two directions: disease associated symptoms such as sleepiness, feeling tired, weakness, losing appetite, etc., which all can be found in depression and can be connected to alteration in the immune system functioning, while also being observed in most of general infectious states induced by different causes. Most of these symptoms are mediated by the hypothalamus[7,8]. It is clear today that, besides immune reactions, immune system is also included in the neuropathologic processes[9]. Major depressive disorder (MDD) is a psychiatric disorder that is presumed to be correlated with changes in the immune functioning[10]. Maes *et al.* suggest a model of major depression which implies that it is correlated with the activation of inflammatory response[11-14]. According to this model or so-called 'cytokinetic hypothesis of depression', major depression can be considered as a psychoneuroimmune disease in which peripheral immune activation (through omitting inflammatory mediator) is responsible for numer-

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ous behavioral, neuroendocrine and neurochemical changes that are correlated with psychiatric state. The initial interest in cytokines in mood disorders was provoked by the occurrence of depressive symptoms observed in patients administered purified or recombinant cytokines as well as by the increase in the peripheral level of proinflammatory cytokines in mood disorders[15]. However, it remains unclear whether the increase in cytokines contributes to disorder development or it occurs as a secondary sequel of disease. Maes *et al*. have initially reported on the increase in plasma interleukin-1 (IL-1) and IL-6 concentrations in people suffering from MDD[16]. Levine *et al*. report on a high concentration of IL-1ß, low concentration of IL-6 and normal level of tumor necrosis factor alpha (TNF-α) in cerebrospinal fluid of 13 inpatients with uncured depression in comparison with a group of healthy volunteers[17]. Many studies report on major depression to be correlated with the increase in circulating levels of cytokines or their soluble receptors, including IL-2, soluble IL-2 receptors, IL-1ß, IL-1 receptor antagonist, IL-6, soluble IL-6 receptors and interferon gamma (IFN-γ)[11]. However, not all researches are consistent. One of the limitations in measuring cytokine concentrations is that cell activity caused by cytokines also leads to the release of soluble receptors (which inhibit biological activity of cytokines), although their circulating level does not influence functioning of the organ involved. In the same way, differences in the circulating concentrations of any specific cytokine between the subject groups need not be significant.

Immune modifications, including changes in IL-6 levels, have often been observed in MDD during treatment with selective serotonin reuptake inhibitors (SSRIs)[18,19]. Current literature lends further support to the view that major depression is associated with a proinflammatory response, as indicated by elevation in C-reactive protein (CRP) and cytokines such as IL-6 and TNF-α. Antidepressants suppress the inflammatory response. Most, although not all, studies support a link between depression and inflammation[20,21]. The aim of this study was to examine the possible differences and changes in the concentrations of proinflammatory cytokines IL-6, TNF-α and CRP between the group of healthy subjects and group of subjects suffering from major depression before and after one-month antidepressant treatment. The possible differences in IL-6, TNF-α and CRP changes in subjects who did and did not respond to antidepressant therapy was also examined.

Subjects and Methods

Subjects

The study was conducted at University Department of Psychiatry, Sestre milosrdnice University Hospital Center in Zagreb during 2009 and 2010. The study included a control group of healthy subjects (n=36, 20 male and 16 female) and a group of subjects with major depression (n=38, 16 male and 22 female) treated at our outpatient department or as inpatients (stationary or day hospital). Control group consisted of students and employees of the Department. They were clinically examined, laboratory analysis and psychological assessment and testing were conducted, and they filled psychiatric scales for depression; thus the subjects not meeting the control group criteria were excluded.

The aim and purpose of the study were explained to all study participants and they signed the informed consent for participation in the study. Those who refused to sign it were excluded, and so were patients with psychiatric or any other somatic comorbidity (diabetes, arterial hypertension, overweight, etc.). Study subjects were aged 25 to 55.

Methods

The data important for the criteria of depression were collected by patient history and heterohistory (family and relatives). The possibility of 'false-positive results' was ruled out because we did not include patients with diagnoses and therapies that could influence the concentrations of inflammatory markers.

We used a structured questionnaire that consisted of sociodemographic and history variables, e.g., sex, age, family history of MDD, disease duration, disease episode duration, overall number of MDD episodes, time between the episodes, age at the first episode onset, and response to antidepressant pharmacotherapy.

The patients meeting the MDD criteria according to DSM-IV-TR[22], additionally evaluated with the Mini International Neuropsychiatric Interview

(MINI)[23] and Hamilton Rating Scale for Depression[24], were included in the study and signed the informed consent. Their blood samples were collected and then they were administered antidepressant therapy (SSRI; escitalopram, alfa-2 adrenergic antagonist, and mirtazapine, 5-HT2A, 5-HT2C and 5-HT3 serotonin receptor antagonist). Blood samples were also collected from MDD patients after one month of antidepressant therapy and the parameters listed below were analyzed. On each occasion, blood sampling was accompanied by clinical psychiatric assessment of depression and therapy course (with questionnaires and scales).

MINI is based on DSM-IV-TR criteria and it was used to diagnose MDD and to exclude other psychiatric disorders. Using MINI, we defined the subtype and complexity of MDD, the course of disorder and therapeutic response. We also used Hamilton Rating Scale for Depression, Hamilton Rating Scale for Anxiety, Clinical Global Impression (CGI), and psychological assessment and testing.

Blood samples from cubital vein for analysis of inflammatory markers were also obtained from control group. Study participants were asked to fast for 12 hours and to rest for half an hour before blood sampling. Blood samples were collected in the morning, around 8.00 AM. Serum was separated by sample centrifugation, frozen and stored at -20 °C until determination of inflammatory markers (IL-6, TNF-α and CRP).

These inflammatory markers were determined when study patients presented for treatment, before antidepressant administration (day 0) and at 30 days of antidepressant therapy. On both occasions (day 0 and day 30), besides inflammatory markers, all the psychiatric scales described above were applied, so that we could compare the possible changes in inflammatory markers with psychic parameters on these scales.

IL-6 and TNF-α were determined by the automated EURO/DPC chemiluminescence assay (Diagnostic Immulite Products Corporation, Gwynedd, UK). Analytical sensitivity of the method is 1.7 pg/mL for TNF-α and 2.0 pg/mL for IL-6. The automated chemiluminescence procedure (DPC Immulite device) has expanded diagnostic applicability of the results obtained. In the automated and computerized procedure, all phases of determination are performed in one reactive container. Different antibodies are connected to the ball placed at the bottom of the reactive container. The device drops the determined volume of clinical sample into the reactive container. In this way, the antigen from the sample gets in touch with the suitable antibody connected to the ball. During incubation, they connect to each other. This is followed by rinsing with a buffer, along with fast rotation around the axis while the buffer is removed to the respective chamber. Then another antibody marked with enzyme is added. After rinsing, luminogenic substrate is automatically added. The enzyme separates the substrate by giving it a glowing chemical combination. The samples travel on a movable tape to the luminometer reader. The results get printed. If the sample does not contain a tumor marker or the cytokine does not create an immunocomplex, the substrate added will not produce glowing in the reactive container.

CRP was determined on a Beckman Coulter autoanalyzer (Olympus Optical Co., Ltd., Tokyo, Japan) by use of the immunoturbidimetric test for CRP level in human serum and plasma and reagents produced by Beckman Coulter, Inc., Brea, CA, USA.

Testing procedure: when the sample is mixed with R1 reagent (buffer) and R2 reagent (antiserum solution), CRP reacts specifically with antihuman antibodies to CRP to form insoluble aggregates. The absorption of these aggregates is proportional to the sample CRP concentration. Beckman Coulter analyzers automatically calculate CRP concentration in the sample. The results are expressed in mg/L. The reference interval for adults is <5 mg/L.

Results

Data were statistically analyzed with the SPSS for Windows 8 software (Chicago, USA). The χ^2-test and Mann-Whitney test were employed for nonparametric data. Spearman correlation for nonparametric variables was used to analyze association between the concentrations of inflammatory markers (IL-6, TNF-α and CRP) and values on Hamilton depression and anxiety scales before and after antidepressant therapy in the group of depressive patients. The level of statistical significance was set at 5% ($P \leq 0.05$).

Table 1. Descriptive parameters and differences between control group (n=36) and group of major depressive disorder (MDD) patients (n=38)

	Patients with MDD M±SD	Control group M±SD	Mann-Whitney test; *P*
CRP	7.5±15.6	1.8±4.2	MWt=54.500; *P*=0.001*
IL-6	10.1±22.0	1.8±1.1	MWt=52.000; *P*=0.001*
TNF-α	12.4±4.1	5.3±1.6	MWt=3.500; *P*=0.001*
Hamilton 1 depression (>22)	26.1±4.3		
Hamilton anxiety (>25)	25.4±5.1		
Duration (months)	4.8±4.1		

MWt = Mann-Whitney test; **P*=statistical significance (*P*<0.05); M = mean; SD = standard deviation

Figure 1 shows serum CRP variable in the group of MDD patients on the day they presented to the hospital and on day 30 of antidepressant therapy (marked with 2); CRP level was significantly lower (*P*=0.011) after antidepressant therapy.

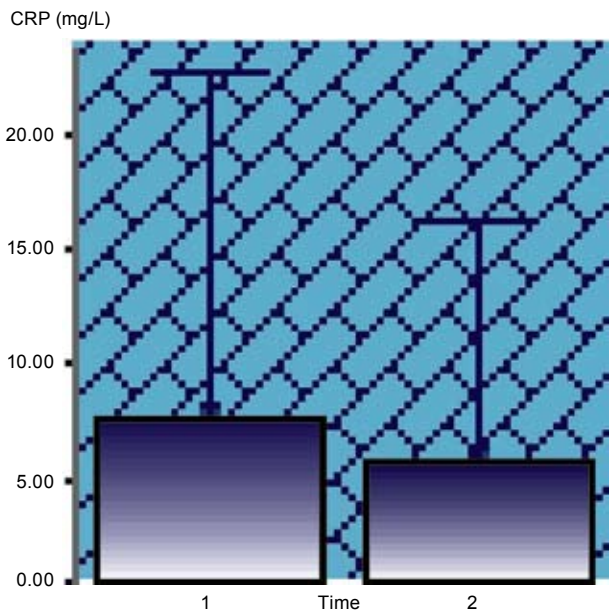

Fig. 1. C-reactive protein (CRP) in the group of major depressive disorder patients (n=38) on day 0 (1) and day 30 of antidepressant therapy (2).

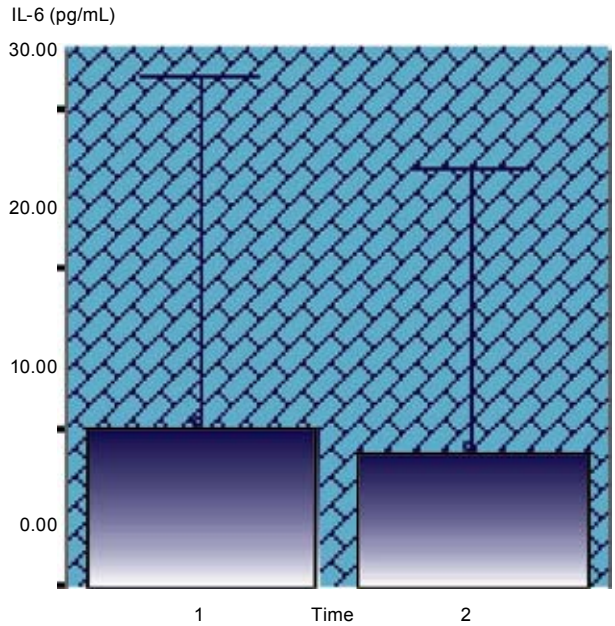

Fig. 2. Interleukin-6 (IL-6) in the group of major depressive disorder patients (n=38) on day 0 (1) and day 30 of antidepressant therapy (2).

Figure 2 shows serum IL-6 variable in the group of MDD patients on the day they presented to the hospital and on day 30 of antidepressant therapy; there was no statistically significant difference between IL-6 level on day 0 and day 30 of antidepressant therapy (*P*=0.483).

Figure 3 shows serum TNF-α variable in the group of MDD patients on the day they presented to the hospital and on day 30 of antidepressant therapy; there was no statistically significant difference between TNF-α level on day 0 and day 30 of antidepressant therapy (*P*=0.646).

Figure 4 shows the Hamilton depression scale results in the group of MDD patients on the day they presented to the hospital and on day 30 of antidepressant therapy; the results on the Hamilton depression scale were significantly lower after antidepressant therapy (*P*=0.01).

Figure 5 shows Hamilton anxiety scale results in the group of MDD patients on the day they presented to the hospital and on day 30 of antidepressant therapy; the results on the Hamilton anxiety scale were

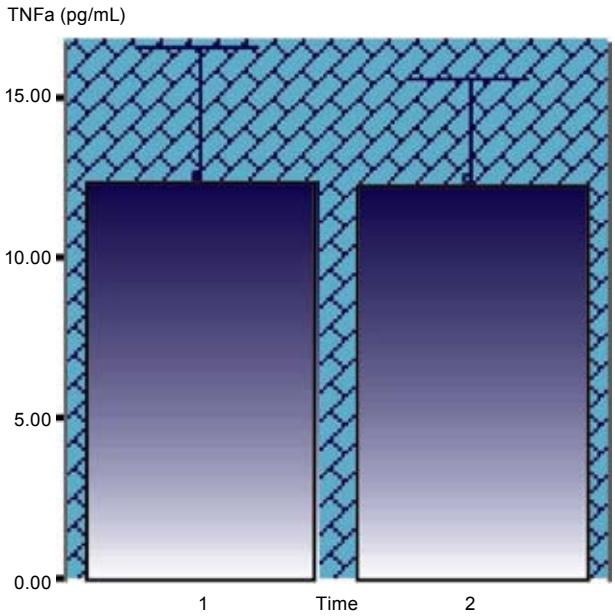

Fig. 3. Tumor necrosis factor alpha (TNF-α) in the group of major depressive disorder patients (n=38) on day 0 (1) and day 30 of antidepressant therapy (2).

also significantly lower after antidepressant therapy (P=0.01).

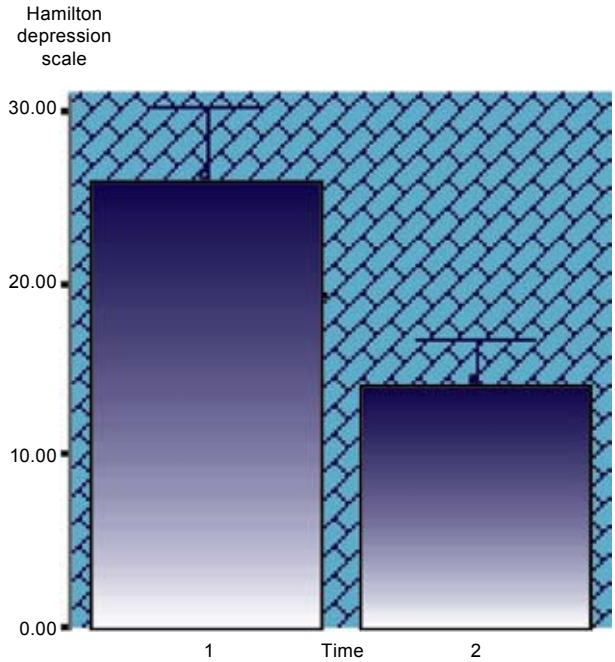

Fig. 4. Hamilton depression scale results in the group of major depressive disorder patients (n=38) on day 0 (1) and day 30 of antidepressant therapy (2).

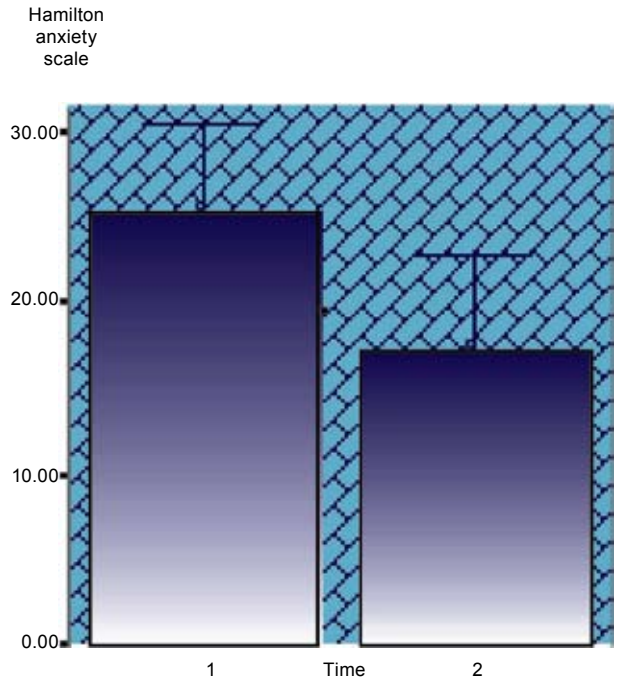

Fig. 5. Results on Hamilton anxiety scale in the group of patients with major depressive disorder (n=38) on day 0 (1) and day 30 of antidepressant therapy (2).

Discussion

Results of this study showed that there was a statistically significant difference in inflammatory markers (CRP, IL-6 and TNF-α) between the group of MDD patients and control group of healthy subjects; these concentrations were higher in the former. For comparison, Maes *et al*. report on the increase of IL-6 concentration in people with MDD[16]. Levine *et al*. report on low IL-6 concentration and normal TNF-α level in the CSF of 13 inpatients with uncured depression in comparison with a group of healthy volunteers; however, their sample was very small[17]. There are other studies reporting on major depression to be correlated with an increase in the level of circulating cytokines or their soluble receptors, among them IL-6 and soluble IL-6 receptors[11]. Yoshimura *et al*. found that plasma levels of IL-6 and TNF-α were significantly higher in the depressed group than in the healthy control group[25].

A statistically significant difference was also found in the concentrations of the CRP inflammatory marker determined in MDD patients before and after antidepressant therapy. This difference suggests that

the inflammatory marker CRP, which was higher in MDD patients compared to control group and lower after than before antidepressant therapy in the former, has an important role in the etiology of depression, as also reported from other studies[9,26,27]. Our results are consistent with the "cytokine hypothesis" of depression[9,28,29] and with some other studies[15,16,20,21]. The significant difference in CRP indicates the importance of this acute phase inflammatory reaction protein as one of the very valuable and definite markers of depression. MDD is associated with some somatic diseases that are the leading cause of morbidity and mortality in the today's world population. Previous researches have shown that the risk of cardiovascular and cerebrovascular diseases, which cause and increase inflammation, is significantly higher in patients with depression than in healthy people[30]. Atherosclerosis is basically also an inflammatory process, so depression could be correlated with the risk of cardiovascular diseases through the mechanism of elevated CRP as a marker of the low level system inflammatory reaction activity[30]. Results of this study undoubtedly demonstrated statistically significantly higher CRP levels in MDD patients as compared with the group of healthy subjects, suggesting that the previously described inflammatory process developed from the onset of the disease through continuously increased CRP. In this study, the factors associated with the possible CRP increase in MDD subjects were excluded by differential diagnosis (connective tissue disease, carcinoma, myocardial infarction, infection, systemic lupus erythematosus, rheumatic arthritis, tuberculosis, rheumatic fever, bacterial pneumonia, pregnancy, etc.). So, the finding of increased CRP in MDD subjects referred to the possible mediating role of acute inflammatory reaction in the etiology of depression. Accordingly, it is valuable information that the patients' CRP concentration was reduced after one month of antidepressant therapy and this result is definitely worth of further studying. In addition, increased levels of the inflammatory markers IL-6 and TNF-α were measured in the group of MDD patients. Other studies have shown that proinflammatory cytokines (IL-1, TNF-α and IL-6) can influence mood and cognitive functions, thus contributing to anxiety, depression and helplessness[31]. Our results also speak in favor of these results. Analysis of serum CRP values in MDD patients on day 0 and day 30 of antidepressant therapy revealed that antidepressants significantly decreased CRP concentration, thus proving that antidepressants strongly inhibit this proinflammatory protein. If we try to define the mechanism of this action, the probable answer would be modulation because antidepressants cause changes in the neurotransmitter activity, thus influencing the proinflammatory markers including CRP, as also suggested by Maes[32]. CRP is an acute phase protein found in the blood and its blood level increases in response to inflammation. As member of the group of inflammatory reaction acute phase reactants, the level of CRP rises constantly during the presence of inflammation in the body. This increase is associated with the increase in plasma level of IL-6, which is induced by macrophages. It grows above the normal values within six hours and reaches peak values within 48 hours. CRP is a marker of inflammatory reaction and a useful indicator in the assessment of disease progress and therapeutic efficacy.

We also studied the effect of escitalopram, a SSRI, and mirtazapine, an alpha 2 adrenergic antagonist, and 5-HT2A, 5-HT2C and 5-HT3 serotonin receptor antagonist, considering that these two antidepressants have in many ways different mechanisms of action than those earlier described. Our study showed that the levels of the proinflammatory cytokines IL-6 and TNF-α were not changed one month after therapy introduction. In order to explain these results, a wider context of the current knowledge about the etiology of depression should be observed[33-35]. Proinflammatory cytokines are strongly released from macrophages in their activated form at the periphery and in the brain[36].

One-month antidepressant therapy led to some therapeutic results in terms of alleviation or partial remission of the symptoms of depression, but the period must have been too short for the possible changes in the concentration of proinflammatory cytokines IL-6 and TNF-α to become evident. However, the decrease in the concentration of the proinflammatory CRP pointed not only to the importance of the mechanism of antidepressant action, but also to the possibility of interaction of anti-inflammatory cytokines. Today, it is well known that many antidepressants increase the release of endogenous cytokine antagonists, such as antagonists of interleukin-1 receptor and interleu-

kin-10 as anti-inflammatory cytokine[4,21,33]. Evidence also shows that different kinds of antidepressants act as cyclooxygenase inhibitors, thus decreasing the concentration of inflammatory prostaglandins in the brain and the harmful influence of inflammatory changes on the neurotransmitter function. The overall sum of Hamilton scale values was significantly different in patients before and a month after the introduction of antidepressant therapy. Early therapeutic response at one month of antidepressant therapy initiation was followed by a decrease in CRP concentration, objectifying the partially positive inflammatory-immune response to antidepressant therapy through Hamilton depression and anxiety scales.

Conclusion

Our study results demonstrated a statistically significant difference in the levels of inflammatory markers (CRP, IL-6 and TNF-α) between the group of MDD patients and control group of healthy subjects; these concentrations were higher in the former. A statistically significant difference was also found in the concentrations of the inflammatory marker CRP before and after antidepressant therapy administered to MDD patients; CRP was lower after taking antidepressants. IL-6 and TNF-α were not statistically different after one month of antidepressant therapy. The questions and conclusions ensuing from these results would certainly involve implications and use of the given knowledge. In other words, the question most frequently posed after this and similar studies is: can the inflammatory markers really be used as dependable and clear markers of depression, considering that they represent significant or even key factors in the etiology of depression? The answer is partially affirmative because diagnostic objectifying and clinically confirmed depression today represents a clear clinical entity considering the diagnostic methods currently available. Still, like biological markers, assessment of inflammatory markers can be additionally performed to confirm the diagnosis of depression, especially if the clinical symptoms and signals suggestive of depression are insufficient to make the diagnosis of depression based on diagnostic methods available. The present study demonstrated that the values of inflammatory markers differed between healthy subjects and subjects suffering from depression, thus providing evidence that additional diagnostic work-up can definitely include determination of inflammatory markers in patients suffering from depression. These results confirmed the efficacy of antidepressant therapy in the treatment of depression. The more so, our results pointed to the possible role of inflammatory markers in the etiology of depression, a very complex psychopathological entity, where the interaction of external, genetic and biological factors leads to the development and manifestation of the disease.

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Sažetak

POVEZANOST UPALNIH BILJEGA, ANTIDEPRESIVA I DEPRESIJE

D. Crnković, D. Buljan, D. Karlović i *M. Krmek*

Cilj ovoga istraživanja bio je ispitati ulogu upalnih faktora u mehanizmu nastanka depresije. Analizirane su koncentracije upalnih čimbenika između skupina zdravih ispitanika i ispitanika oboljelih od depresije pri dolasku i mjesec dana od početka liječenja antidepresivima u potonjoj skupini. Temeljem razlika u koncentracijama navedenih čimbenika željelo se potvrditi njihovu ulogu u nastanku depresije i objasniti mehanizam nastanka depresije. Time bi se uz proširivanje spoznaje o uzroku nastanka depresije mogle primijeniti i nove metode liječenja i dijagnostike depresije. Ovim radom pokazano je postojanje statistički značajne razlike u koncentracijama upalnih faktora (CRP, IL-6 i TNF-α) između zdravih ispitanika i onih oboljelih od depresije. Navedene koncentracije su bile više kod depresivnih ispitanika. Nadalje, nakon terapije antidepresivima zabilježena je statistički značajna razlika u koncentraciji CRP u odnosu na početak liječenja, tj. CRP je bio niži nakon terapije antidepresivima. Dobiveni rezultati govore u prilog učinkovitosti terapijskog djelovanja antidepresiva u liječenju depresije kroz snižavanje koncentracije ovoga upalnog čimbenika.

Ključne riječi: *Depresija; Citokini; Mehanizam djelovanja antidepresiva*