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DEPRESSION AND HEART DISEASES: LEADING HEALTH PROBLEMS

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SUMMARY

Depression is the most common psychiatric disorder in the world population and the most frequent mental disorder in a primary health care. Unrecognized and untreated depression is associated with a poor outcome of treated chronic diseases which co-exist with depression. Depression and cardiovascular diseases are bidirectional related conditions, risks are for each other, and they often co-exist. Depression is a common disorder in cardiovascular patients with a prevalence of 20% to 45%, which is much more frequent than in the general population. In cardiac patients with acute myocardial infarction, depression occurs three times more often than in the general population. Depression has a direct effect on the pathophysiological changes of various organ systems, changing the values of blood pressure, heart rate, vasomotor tone, vascular resistance, blood viscosity and plasma volume. The potential mechanism for developing heart disease in depressed patients includes hypothalamic-pituitary-adrenal gland dysfunction, increased proinflammatory and prothrombotic factor activity, reduced omega-3 fatty acids, reduced heart rate variability, smoking, physical inactivity, reduced mood, self-esteem and self-efficacy.

Key words: *depression - coronary heart disease – comorbidity - self-efficacy*

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Introduction

Depression is the most common psychiatric disorder in the world population and the most frequent mental disorder in a primary health care (Williams et al. 2017). It is ranked fourth in the cause of disability due to illness with constant growth tendency (Stojanović-Špehar et al. 2013). According to the World Health Organization, it is estimated that in 2020 depression will be in the second place of public health problems, next to cardiovascular diseases (CVDs) (Williams et al. 2017, Stojanović-Špehar et al. 2013). This mood disorder is present in all cultures, regardless of sex, age, social environment and also it occurs in animals (Lang et al. 2013). It is characterized by bad mood, feeling of sadness, gloom and emptiness (Stojanović-Špehar et al. 2013). Depression is a severe illness with immense mental suffering, tendency to recurrence, and often begins after a negative life event and is most commonly recognized among patients in a primary health care (Stojanović-Špehar et al. 2013). Despite that, two thirds of depressive patients are presented with somatic symptoms, such as, headache, low back pain or chronic pain (Williams et al. 2017). Depressive disorder is accompanied by significantly poor mood and loss of possible enjoyment in everyday things and activities (Stojanović-Špehar et al. 2013). In addition to depressed mood, it is also featured by loss of interest and satisfaction, loss of self-confidence and self-respect, guilt, sleep disturbances, increased or decreased appetite, decreased concentration, tiredness and depreciation (Stojanović-Špehar et al. 2013, Lang et al. 2013). Unrecognized and untreated depression is associated with a lower quality of life, increased risk of suicide and poor outcome of treating chronic diseases which co-exist with depression (Williams et al. 2017). In contrast to the non-depressed patients, depressive patients have an increased mortality with the relative risk of 1.81 (Williams et al. 2017).

Depression is a common disorder in cardiovascular (CV) patients with a prevalence of 20% to 45%, which is much more frequent than in the general population (Jakovljević et al. 2013). Depressive episodes can often be overlooked in cardiac patients (Buljan 2016). Depressive symptoms are rarely neglected in cardiac patients and their manifestation, especially after myocardial infarction (MI) is considered normal condition (Jakovljević et al. 2013). Depressive patients have a double risk of developing CVD, and on the other hand, cardiac patients are at increased risk for the development of depression, which is usually long-term, especially in patients with chronic heart failure (Jakovljević et al. 2013, Buljan 2016). Depression and CVD are bidirectional related conditions, risks are for each other, and they often co-exist (Buljan 2016).

CVDs are heart and circulatory system disorders, which are divided into stroke, coronary heart disease (CHD), congestive heart failure (CHF), arrhythmia and heart valve diseases (Žegura 2010). They are a significant public health problem worldwide and also it can be classified as global epidemic problem (HZJZ 2013). CVDs were cause of death of 17.3 million people globally, according to a World Health Organization in 2008, and the share of CVD in total mortality was 30% (HZJZ 2013). In the EU countries, they are responsible for 42% of total deaths (HZJZ 2013). CVDs are the leading cause of mortality of men over the age of 45 and women over the age of 65 (Jakovljević et al. 2013).

CVDs have reflexive impact on the occurrence and development of depression (Filaković 2014). Most of the studies deal with the onset of depression after MI and CHF (Jendričko 2012). Depression is an important predictor of complications in cardiac patients as it is considered an independent risk factor for coronary artery disease, while other risk factors are under control (Jakovljević et al. 2013, Buljan 2016).

Depression as a risk and prognostic factor for development of heart diseases

Depression is multicausal disease associated with increased risk of tumor disease, vascular dementia, epilepsy, diabetes, and significantly increases the risk of stroke, MI, and CHD (Lang et al. 2013). Despite that, the psychological aspect of organic disease is often overlooked and underestimated in the diagnosis (Shah et al. 2014).

Bidirectional connection between depression and heart disease has been detected (Lang et al. 2013).

Patients with depressive disorder carry a double risk of developing heart disease (Buljan 2016). Increased CV risk of depressive patients indicates increased incidence of MI and CHD, and consequently higher mortality rate (Correll et al. 2017). Depression becomes an independent risk factor for the development of coronary artery disease, in both sexes, if other risk factors are under control (Buljan 2016). Based on numerous scientific studies, it was concluded that the comorbid states of depression and cardiovascular disease are highly probable, and that these two entities often coexist (Topić 2010).

Psychiatric disorders, particularly depression and anxiety, recognized as a risk factor for heart disease have also a significant impact on the recovery and prognosis of cardiac patients (Topić 2010). The relationship between depression and heart disease is not incidental, and the lack of recognition of the coexistence of these two entities and their untimely and improper treatment creates a problem for the patient (Topić 2010).

Patients with a severe mental disorder, such as depression, have a reduced life expectancy of 10 to 17.5 years compared to the general population (Correll et al. 2017) Besides suicide, a shorter life expectancy lies in the fact that high prevalence of heart disease in depressed patients becomes a key promoter of premature death of depressed patients (Correll et al. 2017). Depressive patients are more likely to develop risk habits and behaviors such as smoking, alcohol consumption, excessive body weight, physical inactivity, which are associated with the development of CVD (Shah et al. 2014).

Depression has a direct effect on the pathophysiological changes of various organ systems, changing the values of blood pressure, heart rate, vasomotor tone, vascular resistance, blood viscosity and plasma volume (Lang et al. 2013, Shah et al. 2014). Furthermore, changes in the synthesis and activity of coagulation factors and fibrinolysis, plasma nitric oxide (NO) and platelets, and often observed increased left ventricular mass on the ECG, is frequently observed in depressed patients (Lang et al. 2013, Shah et al. 2014).

In addition to the already mentioned MI and CHD, depression is also associated with the occurrence of cardiac arrhythmias, congestive heart failure, and isolated systolic hypertension which, ultimately, increases the morbidity and mortality of patients (Lang et al. 2013). The potential mechanism for developing heart disease in depressed patients includes hypothalamic-pituitary-adrenal (HPA) gland dysfunction, increased proinflammatory and prothrombotic factor activity, reduced omega-3 fatty acids, reduced heart rate variability, smoking and physical inactivity (Tofler et al. 2017).

The severity of the depressive disorder is determined by the number and expression of the symptoms, and studies have shown that depressed patients with the highest number of depressive symptoms have 40 to 60% increased risk of developing CHD and mortality, in addition to patients with the smallest number of depressive symptoms (Stojanović-Špehar et al. 2013, Tofler et al. 2017). One study has shown that the sudden appearance of depressive episodes in men older than 70 years is associated with increased risk of death from CVD, and also an increased risk of all-cause mortality (Tofler et al. 2017).

Enhanced sympathetic activity, detected in depressed patients, causes irritability and cardiac ventricular ectopic outbreak, and thus lowers the threshold for ventricular arrhythmias (ventricular fibrillation) in patients with existing electrical instabilities and previously ischemic injuries (Shah et al. 2014). Ectopic activity is not increased in depressed patients, but if it is formerly established, then it is strongly associated with mortality of depressed patients compared to non-depressed patients with ectopic outbreaks (Shah et al. 2014). Animal studies have shown that proaritmic factors are a link between psychological disorders and sudden cardiac death (Shah et al. 2014). Experimentally induced psychological stress on animal models with previously existing ventricular arrhythmias decreased the ventricular threshold for ectopic outbreaks and ventricular fibrillation (Shah et al. 2014).

In depressed patients was observed a decreased level of heart rate variability (HRV) (Shah et al. 2014). Reduced HRV is associated with recurrent complications in patients with acute coronary syndrome and a following acute MI (Shah et al. 2014). Depressive patients have elevated sympathetic tone and reduced basal values of NO and its metabolites, which contributes to higher blood pressure and consequent development of systolic hypertension (Lang et al. 2013, Shah et al. 2014).

Depression affects an increased mortality in patients with heart failure (Chapa et al. 2014). In depressed patients with heart failure, there is more frequent deviation in drug adherence and they also have higher rates of hospitalization and mortality (Horwitz et al. 2017). Depressed patients with heart failure have reported aggravation of the symptoms of both diseases, which explains the synergistic association of the pathophysiology of these two diseases (Chapa et al. 2014). Autonomic nervous

system (ANS) dysregulation, observed in depressed patients, is a predictor of progression of heart failure and sudden cardiac death (Chapa et al. 2014). Depression is, therefore, an independent risk factor in the development of CVD, while other risk factors are under control, and even the latent period of depression can slowly lead to CV illness (Buljan 2016).

Heart diseases as a risk and prognostic factor for depression development

Depression is a common disorder in CV patients with a prevalence of 20% to 45%, which is much more frequent than in the general population (Jakovljević et al. 2013). Depressive episodes can often be overlooked in cardiac patients (Buljan 2016). Depressive symptoms are often neglected in cardiac patients and their manifestation, especially after MI, is considered normal (Jakovljević et al. 2013). Cardiac patients are at increased risk for developing depression, which is usually long-term, especially in patients with chronic heart failure (Jakovljević et al. 2013, Buljan 2016).

According to previous studies, 19 to 66% of patients with pre-existing MI develop a mental disorder, most often depressed, with a prevalence of 16 to 23% (Jendričko 2012). Depression is three times more common in patients with acute MI than in the general population (Jendričko 2012).

Pessimistic attitude of cardiac patients is a predictor of greater psychological distress and depression (Jendričko 2012). As stated by Mary A. Whooley, studies of two American cardiologists Friedman and Rosenman, conducted on 862 patients with a history of MI, showed the importance of behavioral counseling (behavioral therapy) in postinfarction period (Jendričko 2012, Whooley 2006). Respondents with suffered MI were followed for 4 and a half years, and along with the administered drug treatment, they were subjected to behavioral therapy, which influenced the negative traits (Whooley 2006). The respondents on the pharmacological and behavioral therapy had reduced prospect of repeated MI and cardiac death compared with the group of patients solely on the pharmacological therapy (Whooley 2006). Protective effect of behavioral therapy on personality traits relates to strengthening active attitude and patients optimism in regards to their own health status and adequate social support (Jendričko 2012, Whooley 2006). Risk factors that potentiate the development of post-infarction depression correspond to risk factors of depressive disorders in other patients, including female gender, a previous episode of depression and single life (Jendričko 2012). Apart from women, generally middle-aged patients are at increased risk of developing depression (Feng et al. 2016). Current knowledge is that younger and middle-aged people experience the greatest stress after the MI (Feng et al. 2016). Years can be a key factor in the development of post-infarct depression because each life span follows different stressors, priorities, and physical education (Feng et al. 2016). Middle-aged people are mostly employed individuals who work and financial care for the rest of the family, but suffered MI changes the physical strength and ability to work (Feng et al. 2016). Limited physical activity and impaired health condition affect perceptions of patients to their own illness, and changed perception affects mental health and possible development of depressive mood (Feng et al. 2016).

After MI patients are forced to change their own habits and activities, and that emphasizes the development of depression or worsens pre-existing depression (Filaković 2014). Furthermore, poor social support, a year-long stressful events and low levels of education emphasize the development of post-infarct depression (Jendričko 2012).

Patients who develop post-infarction depression are less prone to change habits of risky behavior (Feng et al. 2016). Depressive patients do not try to reduce stress, body weight, sedentary lifestyle and smoking habits (Feng et al. 2016). Research suggests that depression after MI decreases quality of life and adversely affects the cardiac morbidity and mortality, and depressed patients with a history of MI die three to four times more often in the first 6 months of MI than those without depression (Filaković 2014, Jendričko 2012).

Every life-threatening condition, including MI, stimulates the hypothalamus to secrete the corticotropic-releasing hormone (CRH), which stimulates HPA axis (Feng et al. 2016). A stressful life event increases the variability of HPA axis activity and changes the response of sympathetic to the stress (Feng et al. 2016). Dysregulation of HPA axis creates a predisposition for depression (Feng et al. 2016). Two-way connection between depression and heart disease, which share the pathophysiological mechanism of origin, affects the prognosis of post-infarction recovery of depressed patients due to the impact of depression on the HPA axis activation, endothelial dysfunction, platelet reactivation and enhanced inflammatory response (Feng et al. 2016). It has been proven that the first two years after MI carry a high risk of developing depression and recurrent MI (Feng et al. 2016). In order to prevent adverse CV events, patients with pre-existing MI should timely determine the level of the underlying psychological distress and predict the possibility of developing a depressive disorder and ultimately ensure appropriate, age and sexual, specific care (Feng et al. 2016).

Apart from MI, chronic illness such as CHF can contribute to the development of depression (Musliu et al. 2013). Symptoms of depression can often remain unrecognized because of their similarity to the symptoms of CHF (Musliu et al. 2013). Some of the characteristic symptoms of both diseases are fatigue, exhaustion, insomnia, reduced concentration and lack of initiative in daily activities (Musliu et al. 2013). Untreated depression is a significant predictor of increased mortality in patients with CHF (Musliu et al. 2013). Patients with CHF NYHA stage III according to rankings (in stage I there are no

symptoms during normal physical activity, and in stage IV appear severe symptoms at rest) have a significant reduction of the quality of life in the field of mental health (Jakovljević et al. 2013, Musliu et al. 2013). Generalized cognitive impairment in patients with CHF, with difficulties in attention and memory, is attributed to changes in the central neurohumoral system of regulation and reduced central perfusion (Musliu et al. 2013). Impaired cognitive performance in CHF can enhance latent tendency of depressive disorder (Musliu et al. 2013). Treatment of depressive symptoms in patients with CHF significantly improves the quality of life, and besides pharmacological therapy, it is recommended to involve other modalities of treatment, for example, psychotherapy and, if necessary, prescribe psychiatric hospitalization (Musliu et al. 2013).

Pathophysiological relationship between depression and coronary heart disease

The complex pathophysiological substrate of increased comorbidity of depression and CHD is the subject of numerous studies and has not been yet completely dismissed (Jakovljević et al. 2013). CHD and depression are multifactorial diseases with many risk factors (Lang et al. 2013, Damjanov et al. 2011). The co-existence of these two entities is attempted to be explained by neuroendocrine, inflammatory and psychodynamic theories, and endothelial dysfunction, platelets, serotonin, folate, homocysteine, ANS and BDNF are cited as possible mediators of their development.

The underlying neuroendocrine theory of the association of depression and CHD results from the hyperactivity of the HPA axis, which is regulating the body's response to stress (Mihaljević-Peleš 2015, Begić 2014). Hyperactivity of the HPA axis is found in almost 60% of depressed patients (Jakovljević et al. 2013). Hypercortisolemia is defined as the main clinical feature of the pathophysiology of depressed patients (Chan et al. 2017). Stressed situations increase glutamate neurotransmission, and glutamate consequently increases the cortisol concentration (Mihaljević-Peleš 2015). Increased concentrations of glutamate and cortisol reduce the volume of hippocampus causing premature death of neurons, i.e. apoptosis of hypochampus cells (Mihaljević-Peleš 2015). The correlation between hypercholesterolemia and depression is also indicated by the fact that the symptoms of glucocorticoid therapy are similar to the depressive symptoms presented in patients with depression (Chan et al. 2017). Prolonged activation of HPA axis and high concentration of its final product, cortisol, become also the promoter of atherosclerosis, increasing the concentration of cholesterol, glucose, free fatty acids and increasing the blood pressure (Shah et al. 2014). Autoimmune and inflammatory conditions are correlated with an increased incidence of depression, and also in depressive patients there is often a low-active chronic inflammatory process (Mihaljević-Peleš 2015, Begić 2014). In depressive patients appear elevated values of proinflammatory cytokines, such as, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), IL-1, soluble receptors of IL-2 and haptoglobin (Lang et al. 2013, Smith et al. 2011). Proinflammatory cytokines in etiopathogenesis of depression have their role in neurotransmitory and neuroendocrine function and synaptic plasticity (Lang et al. 2013). Proinflammatory cytokines can remove serotonin (5-HT) from presynaptic gap and may also stimulate the release of norepinephrine and 5-HT from the brain, which increases the cortisol concentration by their effect on the HHA axis (Mihaljević-Peleš 2015, Begić 2014). Proinflammatory cytokines IL-1, TNF-α, IL-6 contribute to atherosclerotic etiopathogenesis which is defined as chronic inflammatory response of the arterial wall to endothelial damage (Damjanov et al. 2011, Gamulin et al. 2011). The inflammatory response of the artery wall is stimulated by proinflammatory cytokines which promote adhesion of leukocytes and thrombocytes to damaged endothelium, and also stimulated by the entry of lipoproteins into the arterial wall and their oxidation and in the end they stimulate the migration of monocytes and their transformation into macrophages (Jakovljević et al. 2013, Damjanov et al. 2011). Endothelial dysfunction is potentially associated with depression and CHD (Lopez-Vilchez et al. 2016). In atherosclerotic-modified blood vessels due to endothelial dysfunction, the vasodilating response to NO is absent, resulting in vasoconstriction and coronary thrombosis (Jakovljević et al. 2013). Normal blood vessels endothelium reacts to NO, whose release stimulates 5-HT, and thus provides normal flow through the coronary artery (Jakovljević et al. 2013). Endothelial damage is accompanied by increased plasma concentrations of endothelial activation markers (Lopez-Vilchez et al. 2016). Plasmatic activation markers are ICAM-1, VCAM-1, VWF, and their soluble fractions are found in elevated concentrations in atherosclerosis and depression (Lopez-Vilchez et al. 2016). Significantly, it is known that treatment of selective serotonin reuptake inhibitors (SSRIs) has a protective role and a beneficial effect on modulation of endothelial damage (Jakovljević et al. 2013, Lopez-Vilchez et al. 2016). 5-HT plays a key role in the development of depression, as evidenced by reduced concentrations of the major metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), in the cerebrospinal fluid, postmortal reduction of 5-HT and 5-HIAA concentrations in brain tissue of depressive and suicidal patients, and reduced number of serotonin transporters (SERTs) in the brain and thrombocytes of depressed patients (Williams MS 2012). Platelets depot 99% of total 5-HT in its granules, and endothelial dysfunction is promoter of the 5-HT release from the granules, which results in platelet aggregation (Williams MS 2012). Thus, 5-HT plays a key role in platelet reactivity, and in vasomotor tone (Kim et al. 2014). Elevated levels of 5-HT have been found in patients with a number of CVDs (Kim et al. 2014). Increased platelet reactivity is a risk factor for coronary throm-

bosis and acute coronary syndrome (ACS), and is often linked to depression (Jakovljević et al. 2013). Serotonin and thrombocyte dysfunction in depressed patients can convert stable chronic angina pectoris to unstable coronary syndrome (Jakovljević et al. 2013).

Furthermore, folate metabolism disorders and elevated serum homocysteine concentrations are considered to be a significant risk factor for the development of CVD and depression (Trebatickáa et al. 2017). Homocysteine (HCY, 2-amino-4-sulfanylbutanoic acid) is the amino acid produced in the metabolism of methionine as a product of transmethylation reaction, whose high plasma levels influence cellular stability (Jakovljević et al. 2013, Bukharaeva et al. 2015). Hyperhomocysteinemia (HHCY) is a condition in which the homocysteine metabolite concentration is above 10 μmol/L and such condition is considered a risk factor for the development of CVD and depression (Trebatickáa et al. 2017). Methionine is the essential amino acid necessary for the synthesis of S-adenosylmethionine (SAM), which acts as an endogenous antidepressant in humans by increasing the levels of 5-HIAA in cerebrospinal fluid (Stover 2004, Young 2007). The disorder in the metabolism of folate reduces levels of SAM, and, depressive symptoms are considered the most common psychiatric manifestations of folate deficiency (Young 2007, Babić Božović et al. 2014). SAM, as a methylating agent is important in the processes of DNA and histone methylation, and by the transfer of the methyl group is converted to S-adenosylhomocysteine (SAH), which is finally hydrolyzed to adenosine and HCY (Babić Božović et al. 2014). Approximately 50% of the HCY produced in the cells is reversed back into methionine and the remaining 50% HCY is metabolised by the transsulfuration reaction in cysteine (Ma et al. 2017).

HYC has a direct effect on the metabolism of dopamine, serotonin and occurrence of oxidative stress (Kang et al. 2016). Direct inhibition of monoamine metabolism, mediated by HCY, creates the possibility of developing depression (Kang et al. 2016). High levels of HYC and clinical HHCY (above 15.0μmol/l) significantly increase the prevalence of depression after ACS (Kang et al. 2016). Extremely high levels of HCY were found in patients with atherosclerosis and are considered a cause of vascular disorders that results in coronary occlusion (Damjanov et al. 2011, Bukharaeva et al. 2015). HCY is one of the independent risk factors for the development of CHD, and elevated serum levels of HCY are associated with adverse outcome of CHD (Ma et al. 2017). Studies have shown that the highest elevation of HCY serum concentrations is observed in patients with suffered MI, and they are followed by patients with unstable angina pectoris and stable angina pectoris (Ma et al. 2017). Patients with a severe clinical picture of CHD, typically, have higher serum concentrations of HCY-a (Ma et al. 2017). Increase in serum HCY concentration of 3 μmol / L increases the risk of CHD incidence by 10% and elevation of 5 μmol/L increases this risk by 20% (Ma et al. 2017).

Thus, HCY and traditional CV risk factors are synergistically promoters of the emergence and development of CVDs (Ma et al. 2017).

HHCY is associated with endothelial dysfunction of atherosclerotic blood vessels as an indirect factor in the development of oxidative stress, endoplasmic reticulum stress, inflammatory reaction and elevated levels of asymmetric dimethylarginine (ADMA, asymmetric dimethylarginine) (Ma et al. 2017). Increased levels of ADMA cause reduction of endothelial NO concentration and its bioavailability (Ma et al. 2017). NO preservation of blood vessel endothelium prevents inflammatory reactions, cell proliferation and thrombosis development (Ma et al. 2017). Reduced bioavailability of NO results in abnormal thrombosis, vasoconstriction, and stimulates atherosclerotic changes in coronary blood vessels (Ma et al. 2017).

Depression is associated with chronic stress, the condition triggered by ANS. In the state of stress, the sympathetic part of ANS is constantly activated without an adequate response of the parasympathetic (Won et al. 2016). Sympathetic and parasympathetic imbalances stimulate the immune system to activate proinflammatory cytokines, whose excessive activity generates neurotoxic brain tissue changes and vulnerabilities of the neural galaxy network, making the brain more susceptible to depression development (Won et al. 2016). Methods that enhance parasympathetic tonus: meditation, biofeedback and vagus stimulation are considered effective in treatment of depression (Jakovljević et al. 2013, Won et al. 2016).

The brain neurotrophic factor (BDNF) plays a key role in the survival, differentiation and morphology of neurons, prevents apoptosis, supports neuroplasticity and creates new synapses (Shah et al. 2014, Geroulakos et al. 1994). Stress, depression and CHD reduce the levels of BDNF, presented in serum and plasma, on the other hand, antidepressants increase its level (Jakovljević et al. 2013, Williams 2012).

BDNF promotes the neurogenesis of a damaged hippocampus in depressed patients (Jakovljević et al. 2013). In cardiac patients is disclosed BDNF angiogenic effect and increased activity, and BDNF participates in cardiomyocytes recovery in hypoxic conditions (Jakovljević et al. 2013). During experimental research of MI, scientists observed increased expression of BDNF, which resulted in reduced apoptosis of cardiomyocytes (Jakovljević et al. 2013).

The current knowledge of psychosomatic medicine points to the interrelationship between psychological factors and CV system (Bilić 2010). An individual who is unable to express mentally his psychic energy manifests it through somatic symptoms, and the energy of the "invisible" mind reflects visibly through the physical symptoms (Bilić 2010). Long-term mood disorders dispel psychic energy and ultimately become a promoter of somatic dysfunction (Bilić 2010). Psychic factors may sometimes have a greater influence than somatic on the

development of morbidity in CV patients and are linked to CV incidents in hypertensive patients with increased psychological experiences (Bilić 2010). Psychological experiences precede the CV incident, and the incidence of CV incidents in cardiac patients is specifically related to the patient's personality (Bilić 2010).

Depression defines a bad mood, reduced pleasure, a feeling of sadness, emptiness and despondency (Stojanović-Špehar et al. 2013). Studies point to the association of reduced mood, self-esteem and greater somatization with MI (Bilić 2010). Cardiac patients with a history of MI are mostly emotionally unstable, sensitive and withdrawn individuals with communication problems (Bilić 2010). Possession of negative psychic energy can be symptomatically describe as "carry the burden on the heart" or "feel the pain in heart" (Morscgitzky et al. 2006).

Retention of negative emotions in depressed patients often results in MI, due to discharge of negative psychic energy in a heart attack (Dethlefsen et al. 2011). Thus, negative emotional situations can adversely affect the heart rhythm, and lead to falling out of normative equation (Dethlefsen et al. 2011).

Some studies have shown that assertive behavior and positive emotions have been associated with better CV health (Šagud et al. 2017).

Resilience is defined as a set of protective factors that have an impact on the relationship between a traumatic stress, illness and positive outcomes and it is significant factor for better and successful treatment of CVDs (Šagud et al. 2017).

Resilient people potentiate more positive emotions and cognitions to recover from traumatic experiences effectively and find positive meaning in past events (Šagud et al. 2017). Self-efficacy, a component of resilience, is negatively related to myoglobin and troponin after the MI, suggesting that it can decrease the appearance of the MI by affecting the inflammatory response system and in the end shows a protective effect on CV health (Šagud et al. 2017). Furthermore, resilience and cardiac vagal tone interact synergistically during the period of stress recovery, and, higher vagal tone is connected with more endurance under stressful and traumatic events (Šagud et al. 2017).

To conclude, positive emotions, cognitions and resilience in CV patients result in higher satisfaction and better quality of life (Šagud et al. 2017).

Treatment of depressive cardiac patients

Timely diagnosis and treatment of depression in cardiac patients is essential (Liu et al. 2017). Depressive symptoms in cardiac patients are often masked behind various somatic symptoms (Jakovljević et al. 2013). Cardiac patients often complain to symptoms of fatigue, insomnia, irritability, and atypical precordial pain, and in this case, it is necessary to exclude the occurrence of depression (Jakovljević et al. 2013). The goal of treating depressive episodes in cardiac patients is the withdrawal of all depressive symptoms which are presented (Novak et al. 2016). Incomplete treatment of depressive symptoms or persistence of residual symptoms increases the risk of developing chronic depression (Novak et al. 2016). The untreated depressive episode maintains an unfavorable emotional state of the patient, which has an adverse effect on the further course of the CVD, and accelerates its progression by creating a vicious circle (Žegura 2010). Treatment of depression is one of the key factors in the clinical management of hospitalized cardiac patients (Novak et al. 2016).

Treatment of depressed cardiac patient consists of several therapeutic modalities (Novak et al. 2016). In addition to pharmacological therapy, it is necessary to include patients in cardiac rehabilitation programs, physical programs and provide psychotherapy (Novak et al. 2016). Psychotherapy of depressive cardiovascular patients includes supportive therapy, cognitive-behavioral therapy and interpersonal psychotherapy (Novak et al. 2016).

The patient at the time of illness and reconvalescence passes through three critical stages of an impact on his mental health (Žegura 2010). The first phase is the phase of acute illness in which the actions and behavior of the complete health personnel have an impact on the mental health of the patients (Žegura 2010). The second stage starts after leaving the hospital, and family adjustment to a sick member is extremely important for his recovery and return to normal life (Žegura 2010). Social support for the patient has protective influence on the mental and physical health of the patient (Smith et al. 2011). Social support with its structural component, which refers to the number of members of the patient's social network, emphasizes the emphasis on the functional component, namely the emotional support and acceptance of the sick member by the family and society (Smith et al. 2011). The third phase is the phase of return to work, re-establishing professional relationships with colleagues and superiors, and the phase of determining the actual possibilities of the patient (Žegura 2010).

During psychotherapy, it is necessary to evaluate the psychological profile of the patient (Žegura 2010). Furthermore, it is extremely important to strengthen the patient's motivation to participate in rehabilitation and to learn taking responsibility and caring for their own health (Žegura 2010). It is expected that the patient during psychotherapy adopt acceptable emotional and behavioral responses to stress, as well as cognitive interpretation of the disease (Žegura 2010). The psychotherapist's support is also crucial to the patient in his adoption of the necessary hygienic-dietetic measures (Žegura 2010). The aim of psychotherapy is to restore patients to active life, and delayed recovery of a depressed cardiac patient leads to his disability (Žegura 2010).

Apart from psychotherapy, pharmacotherapy is also necessary, and antidepressants are used to remove depressive symptoms and achieve better quality of life

(Topić 2010). A class of drugs that is safe and effective in cardiac patients are SSRIs, which results in increase of 5-HT in the synapse (Musliu et al. 2013, Folnegović-Šmalc et al. 2004). SSRIs should be prescribed in therapeutic doses until remission is maintained (Musliu et al. 2013). SSRIs have positive effects on normalization of HHA axis activities and acute inflammatory reactions, and both are underlying in the pathophysiological mechanism of the depression and CVDs (Jakovljević et al. 2013). SSRIs normalize HHN axis activity by increasing the number of receptors for adrenal gland hormones in the hippocampus, which strengthens the negative feedback and establishes the homeostasis of the axis (Jakovljević et al. 2013). The immunomodulatory effect of SSRIs is achieved by their influence on the enhancement of anti-inflammatory cytokines, and the reduction of proinflammatory cytokine activity (Jakovljević et al. 2013). Cardioprotective effect of this class of drugs is also reflected in their antiplatelet effect, which is achieved by reducing concentrations of 5-HT in the plasma and ultimately by inhibiting platelet activation (Jakovljević et al. 2013).

SSRIs are by the effectiveness a group of similar drugs, which share a characteristic, as its name suggests, selective inhibition of the 5-HT reuptake (Jakovljević et al 2013, Folnegović-Šmalc et al. 2004). All SSRIs do not have the same structure, and therefore there are differences in pharmacokinetics and pharmacodynamics between these drugs (Jakovljević et al 2013, Filaković 2014). Differences in the clinical sense, among the representatives of the SSRIs, are not statistically significant, except for a group of extremely sensitive patients (Jakovljević et al 2013). SSRIs generally have a good profile of safety and tolerability, and their mild anticholinergic and adrenergic effect is much more favorable than in other groups of psychopharmacists (Folnegović-Šmalc et al. 2004). Typical side effects are transient, manifested as headache, fatigue, nausea and mild tremor, and cardiac side effects are mild and rare (Folnegović-Šmalc et al. 2004).

Early diagnosis of depression in cardiac patients, especially in those with a history of MI, and simultaneous and timely psychotherapy and pharmacotherapy with SSRIs, significantly prolongs the patient's life and improves its quality (Filaković 2014, Topić 2010, Musliu et al. 2013).

Conclusion

Patients with a history of heart disease belong to the group of patients with a higher risk for developing depression. Depression becomes an independent risk factor for the development of coronary artery disease in both sexes if other risk factors are under control. Based on numerous scientific studies, it has been concluded that the comorbid states between depression and cardiovascular diseases are highly probable and that these two entities often coexist. There is evidence of the association between depression and hormone-haematological abnormalities, including HPA axis hyperactivity, platelet abnormality, endothelial dysfunction, high fibrinogen levels, increased left ventricular mass and progression of atherosclerosis. Strengthening the sympathetic component of the autonomic nervous system, due to the hyperactivity of the HPA axis, is a link between the major part of cardiac pathology and neurological disorders.

Depression is associated with an increased risk of coronary heart disease, myocardial infarction, cardiac arrhythmias, congestive heart failure, and isolated systolic hypertension, which increases the morbidity and mortality of patients.

In cardiac patients with acute myocardial infarction, depression occurs three times more often than in the general population.

The timely screening of cardiovascular patients on psychiatric disorders and development of screening tools for psychiatric patients on CV disease should have a positive impact on reducing the prevalence of these diseases among the leading causes of mortality, morbidity and reduced living and working ability of the population.

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