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Depression and Cardiovascular Diseases

Depression is considered to be an independent cardiovascular risk factor and it may worsen the symptoms of already established cardiovascular pathology such as coronary heart disease, chronic heart failure, stroke and hypertension. 3 key psychobiological mechanisms by means of which depression influences cardiovascular system: disbalance in stress response of endocrine system, hyperregulation of autonomic nervous system and immune disorders leading to dysregulation of acute phase proteins and proinflammatory cytokines release. In majority of studies in patients with depression and cardiovascular diseases it was shown that antidepressants improve the symptoms. By the way, in some studies controversial results were obtained. Future studies in this direction with involvement of cardiologists and psychiatrists should be held.

Key words: *depression, cardiovascular diseases, antidepressants.*

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Depression is a common mental illness typically marked by sad and anxious feelings [1]. There are several forms of depressive disorders: major depressive disorder, or major depression; dysthymia; minor depression and some others (psychotic depression, postpartum depression, seasonal affective disorder) [2]. The main symptoms of depression include feeling of hopelessness, guilt, worthlessness, or helplessness, thoughts of suicide, irritability, loss of interest in surroundings, difficulty making decisions, concentrating, sleep and appetite disorders [2]. Depression is often associated with various conditions: arterial hypertension (AH) [3, 4], coronary heart disease (CHD) [2, 4, 5], stroke [2, 4–6], chronic lung disease [5], cancer [2, 4], diabetes mellitus [2, 4], acquired immune deficiency syndrome [2], Parkinson disease [2], and also loss of vision [5] and hearing [5]. Patients who have depression along with another medical illness tend to have more severe symptoms of both depression and the medical illness, more difficulty adapting to their medical condition, than those who do not have co-existing depression [2].

Depression as a risk factor of cardiovascular diseases

Such diseases, as CHD and stroke, were established to be the risk factors of depression in elder age [5]. However, there is also an inverse relationship: depression significantly increases the risk of development of transient ischemic attack and stroke, and this increase is not correlated with other risk factors, including AH and diabetes [4, 6]. In a study of 10 547 women aged 47 to 52 years without stroke in history depression was established to be associated with twofold increased odds of stroke during 12-year follow-up [7]. In a similar study of 80 574 women aged 54 to 79 years without stroke in history presence of depression was associated with increased risk of stroke during 6-year follow-up with hazard ratio 1,29 [8].

Depression is also an independent risk factor of development of cardiovascular diseases [3, 9, 10]. Particularly, depression is a predictor of development of CHD in healthy people [11]. Young people aged 23 to 35 years with high (≥ 16) scores on a scale of Center of Epidemiological studies of USA-Depression, have a significantly higher risk of developing AH compared to those with low (≤ 7) score on this scale [12].

Co-morbid depression complicates course of main illness in patients with cardiovascular diseases [4, 9, 13, 14]. Depression predicts quality of life of patients with CHD, and this relationship is not associated with severity of the disease [15]. When assessing the quality of life of 503 patients with angina pectoris 18 months later after myocardial infarction patients with depression demonstrated significantly lower scores on the Seattle Angina Questionnaire compared with patients without depression [16]. Examination of 5038 patients with verified CHD and/or AH showed that identification clinical signs of depression during first examination

of patients increases risk of cardiovascular mortality by 1,64 times, and risk of total mortality by 1,82 times [17].

Depression is also a risk factor of adverse outcome in patients with acute coronary syndrome [18]. The prevalence of depressive symptoms within one year after myocardial infarction is, according to various sources, from 22,7 to 25.5% [4, 19]. Noticeable, that all categories of depressive symptoms after myocardial infarction, irrespective of duration and nature (persistent, flowing or growing), associated with higher rehospitalization and mortality rates, more frequent angina, more physical limitations, and worse quality of life compared with patients without depression [20]. Depressive symptoms after myocardial infarction are predictors of disaster recovery [21]. Depression after myocardial infarction independently correlates with increased all-cause mortality for 22% and increased risk of cardiovascular events for 13% [22]. Thus, depression is a risk factor for increased mortality in patients with CHD. Furthermore, depression is on par with other serious risk factors, such as myocardial infarction in history or left ventricular dysfunction [4]. Importantly, that somatic symptoms (pessimism, fatigue, sadness, loss of appetite and weight) are associated with increased risk of mortality independent of severity of CHD, compared with cognitive (social withdrawal, work difficulty, loss of concentration) symptoms, that were not found to be predictive of patients with CHD [4].

In a longitudinal study of the severity of depression in 200 patients with myocardial infarction and 190 patients with ischemic stroke in history the following results were obtained. The prevalence of major and minor depressive disorders in the first year amounted to 25% in patients with prior myocardial infarction, and 37.8% in patients with prior ischemic stroke [23]. The most prevalence of depression noted 1 month after cardiovascular events. According to authors' opinion such high prevalence of depression in cardiac patients may be due to common pathogenetic mechanism of damaging of cardiovascular and central nervous systems: 1) vascular hypothesis (generalized damage in vascular system of brain may further influence to the processes of mood regulation); 2) some risk factors common for stroke and myocardial infarction, such as AH, dyslipidemia, diabetes mellitus. Furthermore, damage of small blood vessels of the brain, white matter hyperintensities on magnetic resonance imaging and silent cerebral infarctions may also affect the onset of depression. In addition, less specific mechanisms may also be involved in formation of depression: both myocardial infarction and ischemic stroke are severe stressors, leading to significant consequences for the physical and mental condition of patients. Personal characteristics may also play a role in the development of depression [23].

C. Hornsten et al. examined 4 groups of patients aged 85 years and older: with stroke in the past and experiencing a constant depression; post-stroke and having no depression; experiencing a constant depression with no prior stroke; with neither depression nor with stroke in the past. Mortality rate in the first group was 5 times higher than in the other groups [24].

Many researchers also note the high prevalence of depression in patients with chronic heart failure [25–27]. According to data of one of the studies, main risk factors of developing depression in patients with chronic heart failure in combination with atrial fibrillation are as follows: female gender, low level of education, a NYHA functional class >2, aldosterone antagonists intake [28]. On the contrary, such factors, like body mass index, creatinine level, left ventricular ejection fraction or concomitant medical therapies at baseline (with exception of aldosterone antagonists) didn't affect the risk of depression development [28]. Depression was diagnosed in 54,4% of cases during examination of 68 patients with chronic heart failure aged 43 to 80 years [29]. Notable, that presence of depression significantly reduced health related quality of life. Moderate and severe depression (≥ 10 scores), when asking 402 patients with heart failure using Patient Health Questionnaire, was established to increase risks of hospitalization and emergency department visits nearly by 2 times and total mortality - by 4 times [30]. W. Jiang et al. in their research interviewed on a Beck Depression Inventory of patients ($n = 291$) with heart failure hospitalized as a result of cardiac events. Subsequent observation showed that depression was associated with high risk of all-cause mortality during 1-year follow-up [31]. Notable, that amplification of somatic (not cognitive) symptoms of depression in patients with chronic heart

failure (like in patients with CHD) associated with increased risk of cardiovascular mortality and all-cause mortality during 1-year follow-up [32].

Usually there are 2 groups in most studies of patients with hypertension and depressive symptoms: patients with AH who know about their disease and patients with AH who don't know about their disease. Notable, that participants who knew about their disease, have higher risk of developing mental illnesses compared with patients, who didn't know about their disease [33]. In addition, a weak curvilinear association between systolic blood pressure and distress was observed [33]. These data suggest that the higher risk of distress in patients, receiving treatment for AH, associated with awareness of its diagnosis, rather than having elevated blood pressure [33]. There are few mechanisms, which may explain this effect. Thus, several authors suggest, that awareness of patient of AH and taking antihypertensive drugs may predict the increased sympathetic activity and the development of mental stress [33].

Mechanisms of negative impact of depression in cardiovascular pathology

Beginning with the middle of 1980 there was an opinion, that depression impact only the behavioral aspects of life in patients with chronic diseases (i.e., the decrease adherence to treatment, sleep and nutrition disorders, lack of physical exercises, smoking, alcohol abuse and drug consumption) [4, 34, 35]. Depression is associated with poor adherence to treatment in many diseases [14]. In particular, depressive syndrome has a negative role on adherence to changes of lifeway [9]: patients with CHD and depressive symptoms are significantly less likely to quit smoking than patients without depression [13]. Patients with chronic heart failure also have low level of adherence to treatment [35]: patients with depression control their weight worse than patients without depression [25].

Subsequently, however, the study of three main psychobiological mechanisms, through which depression affects the cardiovascular system, was started:

- disturbance of stress responses of the endocrine system;
- hyperregulation of the autonomic nervous system (that can be expressed, for example, in the impaired heart rate variability);
- disturbance of immune system with dysregulated release of acute phase proteins and proinflammatory cytokines [34].

The disturbance of regulation of the hypothalamic-pituitary- adrenocortical system leads to hypertension, obesity, impaired glucose tolerance and hypercholesterolemia [4]. Depression causes disturbance of serotonergic and adrenergic pathways, accumulation of metabolites (such as homocysteine, platelet activating factor and others) [36, 37]. Serotonin causes different cardiovascular effects, including induction of arrhythmia and vasoconstriction. This hypothesis is in accordance with the results of the study showed that depressive mood is associated with endothelial dysfunction of the coronary vessels in patients without verified CHD [38]. Long-term exposure of the serotonin leads to proliferative processes in the endothelium and thickening of the heart valves [4, 39].

Normally, more than 99% of serotonin is contained in the platelets [37]. The activation of platelets, for example in coronary artery, leads to releasing of serotonin, norepinephrine and, consequently, to activation of sympathetic system. This causes vasoconstriction and increased platelet aggregation and subsequent reduction of blood flow in artery [39, 40]. The described processes underlie the formation of clot – the key pathophysiological mechanism of atherosclerosis, stroke and myocardial infarction [4, 39, 40]. It should be noted, that serotonin causes more expressed platelet aggregation and reaction [37].

In addition, serotonin modulates the immune response and the synthesis of proinflammatory cytokines [41]. It can explain the third mechanism, through which depression acts as a risk factor of development of cardiovascular diseases — the direct influence on nonspecific, adaptive and cellular immunity [4]. It leads to immune-mediated inflammation, which characterized by overexpression of proinflammatory cytokines, mediators of inflammation and contributes to the destabilization of atherosclerotic plaques and induce rupture and thrombosis in the later stages of atherosclerosis. In addition, levels of other inflammatory

markers, such as interleukin-6, C-reactive protein, and tumor necrosis factor- α , are also increased. It leads to chronic inflammation that underlies the pathogenesis of CHD, stroke and many other diseases. Through the influence on the processes of apoptosis and myocardial contractility chronic inflammation leads to the increased risk of adverse cardiovascular events and mortality [4].

Should be noted, that the development of depression and immune inflammation could be genetically determined. So, for example, when genotyping 360 twins, 20 genetic variants of the serotonin transporter gene SLC6A4 were found. According to a study, participants having specific haplotype of this gene demonstrated both elevated IL-6 plasma levels and increased depressive symptoms [41].

Treatment of depression in patients with cardiovascular diseases

Thus, depression and chronic illnesses have a bidirectional relationship in which sustained chronic inflammation, impaired cellular immunity, disruption of neurotransmitter systems relevant to depression, and depressive behavior potentiate each other through a feedback mechanism [4, 41, 42].

Therefore, it is necessary to identify depression on time for prevention [3, 9] and treatment [2] of cardiovascular pathology. First of all, it is recommended to perform screening for depression among patients after myocardial infarction and stroke [17]. Adequate treatment and psychological help are very important for patients with depression [11].

Given the above, we can assume, that timely treatment of depression allows to improve the course and prognosis of cardiovascular diseases [25, 30]. Data of most studies confirm this assumption [39, 40, 43–45]. In particular, treatment of comorbid depression in patients with AH showed following results: 73 patients, received antidepressants and antihypertensive therapy during 24 weeks, had significantly lower values of systolic and diastolic arterial blood pressure compared with initial level. Thus in control group (61 patients received only antihypertensive therapy) such results could not be achieved [43]. In the similar study [44] with lower number of participants (n=64) patients received antidepressants and antihypertensive therapy during 6 weeks demonstrated reducing the severity of depressive symptoms and lowering systolic and diastolic blood pressure. Moreover, in the study group, compared with the control group, greater proportions of participants with 80% or greater adherence both to an antidepressant medication, and to an antihypertensive medication were noted.

R. Ramadan and al. in their interesting study examine the development of myocardial ischemia induced by mental tension in patients with stable angina [45]. 544 patients were asked to take a standardized mental stress test - public speaking. 117 of these patients received antidepressants. Investigators showed that patients receiving antidepressants had a lower risk of myocardial ischemia development compared with other patients. Moreover, this association between taking antidepressants and lower risk of developing myocardial ischemia was significant after adjustment for such risk factors, as depression in history or presence of depressive symptoms at the time of the study.

There are several groups of drugs which are used for pharmacotherapy of depression: antidepressants that inhibit reverse neuronal capture of monoamines; monoamine oxidase inhibitors; atypical antidepressants [46]. The work team of USA National Institute of Heart, Lung and Blood recommends selective serotonin reuptake inhibitors (SSRI) as drugs of choice in cardiovascular patients with depression [35].

SSRI increase serotonin levels in the synaptic cleft and thereby reduce symptoms of depression (there is a deficiency of serotonin in central nervous system in patients with depression). The processes of accumulation, storage and metabolism of serotonin in neurons are very similar to those in platelets. Moreover, the gene responsible for transportation of serotonin is similar in both types of cells [37]. Therefore, SSRIs with high affinity to the serotonin transporters depletes serotonin in platelets and thus reduce their activity [40]. These data are confirmed by the results of some studies [39, 40]. So, W. H. Sauer et al. demonstrated a

significant decrease in risk of myocardial infarction within 3 years when receiving a high-affinity SSRI [40].

The double blind placebo-controlled randomized study of antiplatelet and endothelium-protective properties of SSRI is also notable [39]. Within 24 weeks after identified ACSs 28 patients with depression received sertraline (the drug from the SSRI group) and 36 patients of control group received placebo. 89% of all patients received aspirin, 17% received clopidogrel or ticlopidine, and 29% received either warfarin or coumadin. Plasma concentrations of platelets and endothelial markers were measured at baseline, after 6 and 16 weeks. The results showed that treatment with sertraline is associated with decrease of activation of platelets and endothelium in depressed post-ACS patients. Authors underline that this association doesn't depend on co-administration of antiplatelet regimens.

Many studies have attempted to compare the safety of use of SSRIs and other antidepressants [35, 47]. So, patients receiving SSRI are less likely to have stroke compared with patients taking tricyclic antidepressants [47].

The results of other studies have not confirmed the hypothesis of the necessity of antidepressants reception in patients with cardiovascular diseases [36, 48–50]. So, L.J. Tata and al. established the high risk of myocardial infarction within 28 days after the appointment of antidepressants. But authors explain this association by presence of depression and not by the specific effect of prescribed drugs [50].

Prescription of antidepressants in 162 patients with chronic heart failure was associated with increased mortality (hazard ratio 1,32). However, this study also suggests that increased mortality in patients with chronic heart failure is associated with presence of depression but not with reception of antidepressants [49].

E.L. Fosbol and al. examined 99 335 patients surviving first hospitalization for heart failure from 1997 to 2005. Antidepressants were prescribed to 19 411 patients: 4045 of them received beta-blockers together with SSRI and 980 patients received beta-blockers in combination with tricyclic antidepressants. Prescription of both SSRI and tricyclic antidepressants was established to increase total mortality and risk of cardiovascular mortality. Moreover, co-administration of SSRIs and beta-blockers was associated with a worst prognosis compared with other views of therapy (only SSRI, only tricyclic antidepressants, co-administration of tricyclic antidepressants and beta-blockers). In addition, data of this study showed that receiving of SSRI is associated with decreased adherence to the therapy by beta-blockers and by inhibitors of the renin–angiotensin system. Thus, patients receiving tricyclic antidepressants demonstrated high adherence to the chronic heart failure therapy.

Authors explain the increased risk of total mortality and risk cardiovascular mortality while receiving tricyclic antidepressants by side effects of these drugs and their pro-arrhythmogenic action. In addition, researchers suggest three possible mechanisms of adverse interaction of SSRI and beta-blockers:

- SSRI inhibition of the metabolism of beta-blockers in the liver;
- serotonin direct impact to the myocardium in patients with chronic heart failure, that increases the risk of myocardium fibrosis and lesion of heart valves;
- serotonin activation of platelet aggregation [35].

Systematic review of randomized placebo-controlled studies with using antidepressants for prevention of development or treatment of depressive disorders and mental violations in post-stroke patients showed that prescription of antidepressants decreased symptoms but it had no impact on remission of depressive disorder. In addition, there was no evidence that use of antidepressants prevents the development of depression or improves rehabilitation after stroke [50].

It also should be noted, that we can use herbs for treatment of depression in cardiovascular patients. So, prescription of extract of common St. John's Wort at dose of 15 mg/day has a positive antidepressant effect in patients with AH [51].

Thus, depression often complicates the course and prognosis of many cardiovascular diseases, negatively affects the quality of life of patients. But the challenges of depression treatment in such patients are not studied sufficiently. Further researches are necessary in this direction with participation of both cardiologists and psychiatrists.

Conflict of interests

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