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Review

Depression and Cardiovascular Disease: A Mutual Relationship

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ABSTRACT

The relationship between cardiovascular diseases (CVD) and psychiatric diseases is bidirectional and these two common conditions can occur together. Depression is thought to act as a risk factor in the occurrence and progression of CVD in this association. In this review, the studies examining the interaction between CVD and depression and the pathogenesis of this interaction will be reviewed. The emphasis will be on whether depression is a modifiable factor in CVD and whether its treatment can improve survival. We also aim to draw attention to how depression, which is already on the rise in the general population after the coronavirus disease 2019 (COVID-19) pandemic, has changed with CVD and COVID-19.

Keywords: Antidepressant treatment, anxiety, cardiovascular disease, COVID-19, depression

One of the organs that we use the most when expressing our various emotions and behaviors is our heart. This is not a coincidence and highlights the relationship between the cardiovascular system and psychic structure. Just as psychopathology may be effective in the emergence of CVD, the emergence of CVD may also lead to the development of psychopathology.[1] Psycocardiology emerged as a discipline that examined this relationship and now, as a unit, in CVD patient follow-up works in the same team as the cardiologist and cardiovascular surgeon. Coronary heart diseases are the most important ones in the CVD spectrum. Myocardial infarctions (MI) have been observed to occur 7-10 times more during world wars. The presence of depression is also thought to double the risk of developing new CVD.[2,3]

The first scientific evidence of the relationship between CVD and depression was revealed in 1993 with the work of Frasure-Smith et al.[4] In our country Türkiye, it was found that 35.3% of heart patients had a risk of depression.[5] However, in the presence of other chronic diseases, including CVD, it is difficult to diagnose depression in the patient.[6] Depression is a complex and multifactorial condition, and there is no definitive laboratory test to diagnose it. In addition, some symptoms of depression are nonspecific, and some symptoms, such as fatigue, may be related to depression or may be due to CVD as well as other factors, such as medication side effects.[7] In the event that such a non-specific finding is encountered, the finding should not be considered to be due to depression and should be excluded from the study. In spite of these difficulties, studies have shown that 17-27% of patients with CVD have major depression and 45% have depressive symptoms, and in the presence of CVD, there is a three times higher risk of depression than in the normal population.[8,9] There is a lot of research available showing that depression itself causes the development of CVD. As a result of the evaluation of 21 prospective studies in which 124,509 depression patients were examined, it was determined that depressed patients had a 1.81-fold increased risk for coronary artery disease at 10.8 years of follow-up, and depressive mood increased the risk of developing CVD by 1.5 times, and major depressive disease increased the risk by 2.7 times.[10]

The mechanism of the relationship between depression and CVD has not been fully revealed.

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Different models have been proposed to explain the phenomenon, and the most emphasized is the causal relationship.[11] According to the causality hypothesis, there are three possibilities. These possibilities are: depression causes CVD, CVD causes depression, or a common mechanism causes both diseases together. In the INTERHEART case-control study in which approximately 15,000 patients with acute MI were evaluated, it was determined that as well as the traditional CVD risk factors such as diabetes, hypertension, hyperlipidemia, smoking, abdominal obesity, stress, and depression were risk factors for MI.[12-14] However, Wulsin[15] examined seven parameters in the status of the risk factor for depression and found that depression met four parameters in terms of being a risk factor and that it was acceptable to meet the parameters of specificity and biological probability. It was insufficient to meet the parameter in terms of showing that effective treatment of depression has good effects on the clinical course of coronary disease. However, in order for depression to be causally related to the incidence and prognosis of CVD, it is necessary to show that depression is a 'risk factor' rather than just a 'risk marker' and this has not been fully demonstrated.

Many studies have been carried out for the second hypothesis, CVD causes depression. In the studies of Somberg et al.[16], it was seen that depression developed in 20% of patients after MI and 40% of patients had at least one depressive symptom. In another study, it is stated that the depression accompanying CVD is caused by heart disease.[17] Studies supporting the hypothesis that a common mechanism triggers both pathologies suggest that prolonged exposure to stress can trigger the immune system, leading to chronic inflammation, and consequently depressive symptoms and atherosclerosis in patients.[18] The hypothesis that a common mechanism causes both pathologies is more accepted today.

The risk of developing cardiovascular disease also increases in proportion to the severity of depression.[19,20] When both major depressive disorder and CVD are present, the prognosis is worse for both conditions. This suggests that more attention needs to be paid to mental health to fight CVD, especially in people with depression and chronic stress. There are findings indicating that geriatric depression, which is a general health problem, is also associated with morbidity and mortality in CVD. And more research needs to be done on the relationship between geriatric depression and CVD, which are often accompanied by other comorbidities in older people.[21] There are many studies that examine the relationship between CVD and depression from different angles, and this relationship is undeniable in terms of cause and effect relationship and prognosis.

PATHOPHYSIOLOGY

The existence of a neuroendocrine connection between the brain and other organs suggests that depression may be effective not only for coronary artery disease but also for many medical diseases. When examining the relationship between CVD and depression, genetic factors, biochemical mechanisms, and environmental factors are blamed for pathogenesis. However, it is unlikely that there will be a single simple etiological model to explain this condition. One of the most commonly blamed factors in pathophysiology is heart rate variability. The variability of the heart rate in depression decreases even without coronary disease.[22,23] When the heart rate variability of depressed and non-depressed patients after MI is compared, it is seen that heart rate variability is lower in those who are depressed.[24] It is not yet clear how much of the effect of depression on poor prognosis in cardiac patients is due to heart rate variability. In the study conducted by Copie et al.[25] with 24-hour rhythm holter results in patients undergoing MI after discharge, it was seen that the heart rate of depressed patients was higher than in healthy individuals. In this study, where the left ventricular ejection fraction was also examined in terms of two-year mortality risk, it is stated that heart rate is the most effective factor in predicting cardiac death and sudden death compared to others. The element blamed for decreased heart rate variability is increased sympathetic discharge, parasympathetic inadequate stimulation, or a combination of the two conditions. It is known that heart rate variability is related to the functionality of the autonomic nervous system.

The complex effects of depression on the hypothalamic-pituitary-adrenal axis (HPAA) are also implicated in pathogenesis. The HPAA abnormalities are present in half of patients with major depression, with or without CVD.[26]

This effect occurs especially by increasing plasma cortisol levels with hyperactivation.[27] It is known that cortisol levels increase in depressed patients with chronic stress. An increase in cortisol levels leads to increased cholesterol and triglyceride levels. Cortisol increases the volume by causing sodium retention and there is an increase in peripheral vascular resistance.

As a result, blood pressure rises. An increase in cortisol levels reduces the level of total and intramyocardial potassium, lowers the threshold of ventricular arrhythmias, and accelerates atherogenesis. Each of these is an important risk factor for heart disease. High cortisol levels are thought to aggregate CVD by contributing to diabetes, hypercholesterolemia, hypertriglyceridemia, high blood pressure, and obesity components of the metabolic syndrome.[28] Hyperactivity of the HPAA also leads to increased activity in the sympatho-adrenal system through central regulatory mechanisms and, consequently, to an increase in plasma catecholamine levels. Increased catecholamines in plasma lead to vasoconstriction, platelet activation, and tachycardia, and cause negative effects on the cardiovascular system in the same way.[29]

Genetic Factors: The apparent familial predisposition seen in both depression and CVD has been demonstrated in twin studies.[30,31] Their work with mono- and dizygotic twins revealed that heart disease and hypertension were significantly associated with five depressive symptoms and that this association could be explained by genetics, and that depression and CVD shared a common genetic basis.

Serotonergic Pathway Genes: As a neurotransmitter, serotonin is involved in many psychological processes such as appetite regulation, temperament, anxiety, consciousness, and wakefulness. It has a role in vascular physiological events such as smooth muscle contraction and regulation of platelet aggregation. Decreased serotonergic function in the central nervous system has been shown to increase CVD risk and death by altering the HPAA's response to stress.[32]

Immune System: It is now known that there is a relationship between depression and inflammation. Particular emphasis is placed on increased levels of interleukin-6 (IL-6) and C-reactive proteins (CRP) Inflammation also plays a key role in atherosclerosis.[33] IL-6 gene polymorphism has been studied the most about this subject. The -174C allele, which is formed as a result of G/C conversion in the promoter region of this gene, is associated with increased plasma CRP and IL-6 concentrations, higher blood pressure, and increased CVD risk in male patients.[34]

Psychosocial behavioral factors are also to blame in pathogenesis. But behavioral mechanisms have not yet been identified as a causal model. Biobehavioral mechanisms involving risky health behaviors have been shown to be other mechanisms to blame in the relationship between CVD and depression. These, in turn, affect the development of CVD and its negative consequences. Psychosocial stressors have a direct impact on the stress response system, as well as lead to unhealthy lifestyle behaviors that contribute to CVD. Certain of them are associated with lifestyle and risky health behaviors known to be strengthened by CVD, such as increased smoking, unhealthy food selection, decrease in physical activity, and non-compliance with medical treatment due to the effect of depression.[35]

Loss of hope, an important symptom of depression, has been linked to sudden death in both observational and prospective studies and animal experimentation studies. In one study, those who answered yes to the question "Do you feel sad, disappointed, hopeless (for the last month)?" were twice as likely to risk CVD. Smoking and high cholesterol are also known to be affected by personality structure and stress, which are also risk factors for CVD.[13,18,35]

Physical activity: Regular physical activity, especially as a preventive measure for CVD, is very commonly recommended as it causes a 25% reduction in all mortality rates, including cardiovascular mortality, depressive symptoms restrict exercise, and the desired benefit is not achieved.[28]

Stress: The effect of stress on catecholamines manifests itself in several forms. Cholesterol levels increase, free fatty acids increase, blood pressure rises, the number of heartbeats rises, myocardial contractility and oxygen demand of the heart increase, the threshold of ventricular fibrillation decreases, and platelet adhesivity increases. Stress also increases cholesterol rates. In a study in which monkeys were given a high-cholesterol and low-cholesterol diet and observed their behavior, clearer aggression was observed in those fed with low cholesterol, and they also had lower serotonergic activity in the central nervous system.[34, 35]

Stress leads to an increase in vessel volume. In studies conducted in treatment-resistant hypertension cases, it was found that 15% of hypertension cases were resistant to antihypertensive therapy and this resistance was more frequently linked to intravenous volume load. Studies have shown that the physiological and behavioral effects of repeated stress and hostile interactions prevent the beneficial effects of drugs on plaques in the vessels.[29,30]

Smoking: It has been shown that mortality due to MI decreases in individuals with CVD who stop smoking. A close relationship between depression

and increased smoking is known.[18]

Depressive symptoms lead to a decrease in motivation and it disrupts the patient's compliance with the treatment protocol (medication, diet, exercise). In fact, in some patients, self-destructive attitudes such as resuming smoking, alcohol use, and high-calorie-cholesterol food intake can be observed. The way of thinking, "If I'm going to die, why should I put myself in more trouble?" is common in patients with depression.[30,33]

CARDIOVASCULAR EFFECTS OF ANTIDEPRESSANT TREATMENTS

In order to explain the relationship between CVD and depression, studies were conducted with the idea that if these related conditions were treated, this would improve the progression of the other condition associated with them. In one of the first studies on this subject, Glassman et al.[36] followed a 24-week plan in which sertraline therapy was administered to patients with severe depression who were followed up in the ward with diagnoses of MI and unstable angina within one month. As a result, sertraline after MI was not superior to placebo in preventing cardiovascular events. Similar studies have not shown that treatment of depression in cardiac patients improves cardiovascular prognosis. However, in some later studies, data were obtained that antidepressants may increase the risk of adverse cardiovascular events (stroke, cardiovascular disease, and sudden cardiac death) contrary to expectations. In Whang et al.[37] study it was also found that depressive symptoms were associated with fatal coronary events in women without basal coronary artery disease, while women taking antidepressants had a higher risk of sudden cardiac death. Although it has been suggested that the negative outcome in these studies may be related to more severe depression in those taking antidepressants and may also depend on the period of the depressive episode, the relationship between sudden cardiac death and antidepressant use has not been fully explained. One of the rare studies that the treatment of depression in cardiac patients may have positive effects on prognosis is made by Davidson et al.[38]

The Relationship Between Cardiovascular Medications and Depression

Especially in the use of beta-blockers with high liposolubility, central side effects, and depressive symptoms have been reported.[39] Research on the relationship between statins and depression has shown that statin use reduces depressive symptoms and the risk of developing depression in individuals with CVD.[40]

SCREENING FOR DEPRESSION IN CARDIAC PATIENTS

Since the association between CVD and depression is known, the issue of whether depression screening is required in all cardiac patients and the subject of how to get results from this has been raised. Although current guidelines recommend screening for depression in cardiac patients, there are no definitive conclusions on this issue. There are also studies reporting that treatment for depression may not improve the prognosis in a cardiac patient and that antidepressant therapy may increase cardiac death, so screening is not necessary. According to another study, anxiety, and depression should be screened in all patients with critical atherosclerotic disease.[41,42] Thombs et al.[43] reviewed 11 studies evaluating the need for depression screening in CVD and six studies evaluating depression treatment and they concluded no clinical trial, whether screening for depression in patients with cardiovascular disease improved depressive symptoms or cardiac outcomes. It may be considered that patients who are more at risk than a general screening or who have clinically detected symptoms of anxiety and depression should be referred for professional mental health help. In cardiac rehabilitation, psychosocial interventions including cognitive behavioral therapy, problem-solving therapy, and stress management programs can be applied alone or in combination with other interventions.

THE EFFECT OF COVID-19 ON THE LINK BETWEEN CVD AND DEPRESSION

Coronavirus disease 2019 (COVID-19) social restrictions have emerged as a risk factor that cannot be ignored during this period for mental health issues and especially depression alongside CVD.[44] There is a dangerous association between CVD, depression, and COVID-19. They can all be together and affect each other badly. Chronic inflammation seems to be a common condition in pathogenesis. In one study, an excessive acute response or persistence of systemic inflammation and ultimately activation of the immune system were associated with various cardiovascular, neurodegenerative, and metabolic diseases, cancers, pathologies of the musculoskeletal system, and depression.[45] Although women appear

to be better off for COVID-19 in the short term due to the anti-inflammatory effects of estrogen, they have been worse affected by COVID social restriction conditions, such as depression, reduced physical activity, and worsening lifestyle habits, all of which could affect CVD risk. COVID-19 has had worse effects on women, as depression is also an under-recognized and under-treated risk factor for CVD in women. In addition, studies have shown that the risk of developing long-term COVID in middle-aged women is two times higher.[46] Major depression peaks in young adulthood, which has expanded its framework during the COVID-19 pandemic. Aggregated data have shown us that immune system dysregulation in elderly patients with major depressive disorder is associated with increased CVD. A number of recent studies have been conducted on younger patients with major depression. It was investigated whether this disorder was also present in young major depressive patients without any comorbidities. And increased T-cell mitochondrial reactive oxygen species (T-cell mitoROS), a precursor of immune system dysregulation, were studied in these patients and a significant elevation was seen compared to the group without a major depressive disorder. This led us to conclude that in these young patients with major depressive disease, this test can be considered an early marker of immune system dysregulation.[47-49]

In conclusion, while there are many studies that show the interrelationship between depression and CVD, depression does not meet all the criteria of being a risk factor for CVD. It is also not clear which disease primarily triggers the other. The view that there is a common mechanism in their formation, such as chronic inflammation, which affects both, is more widely adopted. However, it is unlikely that a single, simple etiological cause is to blame. In addition, although depression appears to be related to a poor prognosis in CVD, treatment of depression has not been shown to improve the endpoints of the disease in patients with CVD. Although recommended in some studies, depression screening in all patients with CVD has become controversial and it is more accepted to refer patients with CVD who are at risk or who have depression to a psychiatrist. In addition, an increase in depression was observed during COVID-19, especially in female patients, which worsened the frequency and prognosis of CVD. Especially in the long COVID-19 syndrome, the chronic inflammation process is thought to trigger both conditions and more research needs to be done on this subject.

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