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The Relationship between Depression and Cardiovascular Disease

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ABSTRACT: While there has been extensive research on the link between depression and cardiovascular disease, few reviews have summarized the array of findings. In this literature review, we examined approximately 50 clinical papers and research studies to determine if reducing depression could reduce the risk of having a cardiovascular incident and if reducing the severity of cardiovascular disease could reduce depression. We identified two major mechanisms through which depression affects the cardiovascular system. We present evidence that depression and cardiovascular disease may have a reciprocal relationship. For instance, depression is as much of a risk factor for heart disease as smoking and hypertension. Further, depression is 20% more common in patients after a major cardiac event like a myocardial infarction. In addition, we examine how treating depression could reduce the risk of developing a cardiovascular disease.

KEYWORDS: cardiovascular disease; depression; chronic stress; heart failure

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INTRODUCTION

Mental illness not only influences the psychological aspects of the body, but it can also negatively impact the physical body as a system. For example, depression is a debilitating condition and the leading cause of disability worldwide (Mata D, 2015). This disorder affects an individual's mood with a persistent feeling of sadness, agitation, social isolation, and suicidal thoughts. In addition, it could have physical implications in terms of sleep, energy and appetite disturbance (Health Guide, 2019). Mental illnesses can affect the physical fitness of individuals. For instance, individuals with depression may experience reduced energy and lack of motivation. Further, a study of 51 hospitalized depressive patients showed a correlation between the length of the depressive episode and poorer physical performance (Voderholzer U., 2011). This study demonstrates how mental health has an impact in the entire body, including the cardiovascular system.

Major depression is set to become the leading cause of disability worldwide by the year 2030 (Khalid Faroog, Asghar and Kanwal, 2017). It is established that depression is more prevalent in people who suffer major cardiac events. Depression influences people's behaviors and results in abnormal functioning of the cardiovascular system. Currently, cardiovascular disease is the number one cause of death globally; more people die annually from cardiovascular disease than from any other cause (World Health Organization, 2017). Studies have suggested a possible reciprocal relationship between the two illnesses. The presence of cardiovascular disease in patients with depression, and, conversely, the development of depression after a cardiac disease are common. For instance, patients with heart failure and depression have an increased risk of being readmitted by heart failure exacerbation and, by consequence, suffer a significant increase in mortality risk (Pozuelo, 2018; Jiang, 2007). A study conducted on 374 patients with congestive heart failure showed that patients with major depression had higher readmission and mortality rates compared to patients with mild or no depression. Also, these patients were twice more likely to be readmitted or die within three months to one year after a hospitalization than non-depressed patients (Jiang, 2001). Depression can cause autonomic dysregulation, hyperproduction of cortisol, prothrombotic and proinflammatory states that are commonly seen in the development of heart failure (Silver, 2010). In addition, symptoms of depression are three times more common in patients after an acute heart attack than in the general population (Gebska, 2016). Despite the overwhelming evidence of this relationship, these diseases are rarely treated together. Preventive measures should be taken when one of the diseases is present.

Treatment for depression has been shown to reduce the risk of developing cardiovascular diseases. The combination of pharmacological and psychological treatments appears to be effective in reducing depressive symptoms in patients with cardiac disease and has been shown to have a positive effect during recovery after a major cardiac event. We seek to examine the possible relationship between depression and cardiovascular disease. Our inquiry explores whether mitigating depression could decrease the risk of having a cardiovascular incident and if reducing the severity of cardiovascular disease could reduce depression.

METHODS

To investigate the relationship between depression and cardiovascular disease, a literature review was conducted. PubMed, the UCF Library database, and Google Scholar were searched for clinical papers and research studies pertaining to depression and cardiovascular disease. Key words such as depression, cardiovascular disease, heart disease, hypertension, arrhythmias, and stress were put into each database's respective search engine. Articles containing these selected keywords were collected, analyzed for their relevance, and then selected for inclusion. The searches were limited to studies reported in English between 1987 and 2019.

FINDINGS

Depression and Cardiovascular disease: a bidirectional relationship

Depression is about twice as likely in people with heart disease compared to the general population and, similarly, people with depression present a higher risk of developing heart disease (Harvard Heart Letter, 2016). These figures indicate that the relationship between depression and cardiovascular disease is bidirectional.

There is about an 80% increased risk of developing a heart condition with depression, even if the patient doesn't present a history of cardiovascular disease (Chaddha, Robinson, Kline-Rogers, Alexandris-Souphis, & Rubenfire, 2016). In addition, depression

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after a heart attack is common, especially in patients with drastic procedures such as a coronary bypass. Procedures like this have extensive periods of recovery and can be stressful. This stress has been shown to take a toll on the patient's mental health. After surgery, it is common for patients to have trouble sleeping and present with fatigue; these symptoms are commonly found in patients with depression (Harvard Mental Health Letter, 2009).

How might depression promote cardiovascular disease?

The effect of depression on the body and physical health

The American Heart Association lists depression as a risk factor after a heart attack and as an accelerator for atherosclerosis. One of the main reasons depression contributes to the increased risk for cardiovascular disease is the negative effects it has on patients' lifestyles. Depressive symptoms include anxiety, fatigue, anhedonia (loss of interest in previously enjoyable activities), and hopelessness (Lazarus, Newton, Cohler, Lesser, & Schweon, 1987). Due to some of these symptoms, individuals with depression tend to be less physically active than non-depressed individuals (Paluska & Schwenk, 2012). A study conducted on 106 patients, among whom 48 were depressed, showed that 1/5 of the depressed patients were initially motivated to start regular physical activity. Only 1/4 of these patients completed the whole program. In comparison all nondepressed patients completed the program. The researchers hypothesized that a possible reason for this result was that depression reduces adherence to exercise regimes. Further, all patients who continued with physical activity reported their mood was better, even the depressed patients (Suija, et al., 2009).

Furthermore, a study conducted on 3,486 individuals concluded that depressed individuals are more likely to crave sugar and carbohydrates (Akbaraly, Brunner, Ferrie, & Marmot, 2018). These types of foods could provide a short term benefits, such as comfort, but in the long term, a high level of sugar and carbohydrates in the diet increases the risk for chronic conditions including diabetes, cancer, cardiovascular disease, and more (Akbaraly, Brunner, Ferrie, & Marmot, 2018). Another study showed that men are more susceptible to the effects of sugars on mental health. The study concluded that men who ate 67 grams or more of sugar daily were 23% more likely to develop depression after five years. The researchers did not find any association between the amount of sugar ingested and incidents of depression in women. Although, higher intakes of sugar were correlated to recurrent depression in both sexes (Knuppel, Shipley, Llewellyn, & Brunner, 2017).

Depressed individuals may consume alcohol or engage in substance abuse to improve their mood or escape feeling of sadness, despair or guilt. This method of self-medicating can make depressive episodes more severe by increasing their frequency and intensity (American Addiction Center, 2020). Statistically, depressed individuals are more likely to report substance abuse than individuals without depression. Alcohol dependence is also two times greater in individuals with a history of depression (Currie, 2005). The use of depressants like alcohol can increase feelings of sadness and fatigue. A study conducted on the comorbidity of major depression with substance use showed that drug dependence is four times more prevalent in depressed individuals and increases the chances of having suicidal thoughts. In addition, substance abuse increased the prevalence of depression to 17% (Currie, 2005). Substance abuse increases the severity of the mood disorders by increasing the levels of stress experienced by the individual (Hasin D, 2002). This stress affects the heart and increases the risk of developing cardiovascular diseases.

In general, people with low physical activity, unbalanced diets, and unhealthy substance dependence are more likely to develop major depression and heart-related conditions (Cabello, et al., 2017). A study conducted by Bonnet, Irving and Nony showed that depressive symptoms associated with unhealthy lifestyles are more common in hypertensive patients. The presence of depressive symptoms was significantly associated with unhealthy diet practices such as high caloric intake (Bonnet, Irving, Nony, Berthezene, & Moulin, 2005). This association also included a decrease in physical activity and increased smoking habits. The study showed that the prevalence of depression was 6% higher in woman than in men (Imran Shuja Khawaja, 2009). This gender gap was attributed to unequal power and status, work overload and abuse that women are more susceptible to experiencing (Mayo Clinic, 2020).

Depression on the biological mechanisms of cardiovascular disease

The association between cardiovascular disease and depression influences the normal physiological processes of the body. Specifically, the activation of the sympathetic nervous system and stress pathways

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are linked to unfavorable outcomes for a patient at risk for cardiovascular disease. Also, the psychological stress experienced by people with depression can cause deregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Chaddha, Robinson, Kline-Rogers, Alexandris-Souphis, & Rubenfire, 2016). The activation of the sympathetic nervous system affects the cardiovascular system directly through the "fight or flight" response. During stress, oxygen demand increases. The body reacts by releasing catecholamines, stress hormones that constrict the blood vessels, reduce blood flow, and increase heart rate. This reaction is known as mental-stress-induced myocardial ischemia (MSIMI). Furthermore, a study conducted on 98 patients hospitalized for acute myocardial infarction showed a positive association between depressive symptoms and ischemia. The study evaluated both somatic and cognitive depressive symptoms. Further, patients with coronary artery disease showed an increased inflammatory response to mental stress. This inflammation showed a correlation with abnormal coronary microvascular function, suggesting a possible mechanism of mental stress-induced ischemia (Jingkai Wei, 2014).

In depressed and anxious individuals, this response may become constant. The high dose of catecholamines may cause necrotic lesions in the myocardium. These lesions are usually accompanied with inflammation and fibrous scarring. Further, they may potentially destroy the elastic lamellas and atrophy the wall of large vessels (Haft, 1974). This damage might lead to conditions like atherosclerosis. The basic mechanism for this condition involves the lipid accumulation and inflammatory activation in the vascular wall (Zmyslowski & Szterk, 2017). The damage to the laminar flow in shear stress on the arterial wall triggers the accumulation of lipids and fibrous elements in the arteries. This process, known as atherosclerosis, is the primary cause of heart disease and stroke (Lusis, 2000). These complications can make the heart more susceptible to signals such as changes in heartrate. This deregulation may contribute to the development of serious heart conditions such as hypertension, arrhythmias, platelet activation, and coronary heart disease (Dhar & Barton, 2016).

Stress is related to the cardiovascular system and is part of the proper functioning of the nervous system. Concerns may arise when stress is constant, as this condition affects behaviors and factors that increase the risk for heart disease. Mental stress is one of the many cognitive symptoms that people with depression suffer from. The induced activation of the HPA axis by depression and the stress associated with it increases the release of stress hormones like cortisol (Chaddha, Robinson, Kline-Rogers, Alexandris-Souphis, & Rubenfire, 2016). In small quantities, cortisol prepares the body for physical and emotional stress. In depressed patients, however, cortisol production becomes problematic due to the prolonged stress. Elevated levels of cortisol increase blood sugar, low high-density lipoprotein, and blood pressure. Further, high cortisol levels reduce the ability of the body to fight infections, and increase fat storage in the body (Dienes, Hazel, & Hammen, 2019).

Hypertension is a common condition that can have long-term effects on the body. Uncontrolled high blood pressure increases the risk of serious health problems. Hypertension is often triggered and maintained by mental stress. Stress increases the release and reduces the uptake of norepinephrine (Delgado & Moreno, 2000). Norepinephrine is a hormone and a neurotransmitter that plays a role in circadian rhythms, attention, emotions and memory. Increased levels of norepinephrine are linked with panic attacks, elevated blood pressure, and hyperactivity, while low levels cause fatigue, lack of concentration and sometimes depression (Delgado & Moreno, 2000). Elevated levels of norepinephrine have been found in the plasma and the cerebrospinal fluid of depressed patients (Dhar & Barton, March 2016). Further, a study conducted on 45 individuals with chronic heart failure showed increased mortality in patients suffering from major depression or with norepinephrine plasma levels 40% greater than those of the control group (Gold, 2005). Psychological distress due to severe anxiety, constant stress, and recurring depression can result in the release of epinephrine, which also contributes to the increase of blood pressure and constricts the arteries. During stress, the body releases epinephrine, which triggers the "fight or flight" response (Hormone Health, 2015). Repeated release of epinephrine may lead to plaque disruption, myocardial infarction, and, in more chronic cases, may cause an aortic rupture (Gebska, 2016). Prolonged mental stress has been shown to increase platelet activation and endothelial dysfunction; both conditions are considered early signs of cardiovascular deterioration (Grippo & Johnson, 2009). Depression is also linked to low-grade inflammation and is implicated with increased platelet activity. This condition can increase the probability of the thrombus formation and the rupture of cholesterol-filled plaque (Chaddha, Robinson, Kline-Rogers, Alexandris-Souphis, & Rubenfire, 2016). The constant production

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of stress hormones due to depression activates platelets, making them more likely to form clots in the bloodstream. In fact, depression is associated with raised platelet serotonin levels, promoting clotting (American Psychiatric Association, 1994).

Cytokines are known for causing changes to the central nervous system. Studies have examined the increase of pro-inflammatory cytokines in elderly depressed patients and in women experiencing post-partum depression. In a study conducted by Faroog et al., cytokine levels were directly proportional to the severity of the depression (Khalid Faroog, Asghar and Kanwal, 2017). The cytokine Interleukin-6 (IL-6) has been linked to stress-related disorders such as depression and anxiety. The elevated level of IL-6 in the blood of patients with depression is caused by chronic stress. Evidence suggests that increases of IL-6 also increase stress sensitivity (Hodes, Menard, & Russo, 2016). In addition, there is evidence that inflammation due to IL-6 plays a role in the development of coronary heart disease and atherosclerosis. Elevated levels of cytokines are associated with an increase in blood viscosity and an increase in platelet number activity. Further, IL-6 stimulates activation of the HPA axis; this activation is associated with vascular damage, higher risk of obesity, hypertension, and insulin resistance (Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000).

Depression after a Heart Attack

The American Heart Association recommends patients who have suffered a heart attack be screened for depressive symptoms. Major depression is 20% more common in patients after a heart attack; during recovery, 20% of the patients might suffer from mild depression (Woolston, 2019). The combination of major life stressors contributes to the development of depression. The emotional distress accompanied by the recovery from a heart attack increases the risk of another heart attack or any related cardiovascular disease (Williams, 2011). Once depression is present in the patients who suffered a major cardiac event, it is expected for them to still present depressive symptoms 4 months post-discharge (Dhar & Barton, March 2016).

Treating the Disorder

Depression impacts patients' health, family members and quality of life. Treating depression alleviates the depressive symptoms affecting the body and the lifestyle of the individual. Additionally, treatment decreases the constant stress and anxiety that triggers the release of stress hormones and disrupts the balance of the HPA axis. Treatment has demonstrated improvements in long-term cardiovascular health and increase quality of life. Further, medications, therapy and non-medication interventions such as exercise and meditation have been shown to reverse the cardiovascular changes due to the mental distress (Levine, 2017; Ornish, 1997). Patients suffering from depression who haven't been diagnosed with cardiovascular diseases can benefit from regular exercise, better nutrition, and stress management techniques. These factors decrease the risk of developing recurrent depression and cardiovascular disease.

Various antidepressants are available to manage symptoms of depression, but it is important to evaluate the cardiovascular risk before prescribing (Jiang & Davidson, 2005). The production of effective medications for the treatment of depression and patients with cardiovascular disease has increased over time. Some examples of antidepressants include

Biological Mechanisms	Behavioral Mechanisms
Genetic vulnerability	Low nutritional diets
Enhanced activity of the HPA axis	Lack of exercise
Increase level of catecholamines	Decrease in medication compliance
Mental stress induced ischemia	Poor social support
Increase cortisol levels and other stress hormones	Addictive and harmful activities: smoking, alcohol and illegal drugs
Inflammatory process- increase cytokines levels	Poor coping skills with stressors

Table 1. List of possible mechanisms that may lead to cardiovascular disease

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Reference	Objective	Subjects	Methods	Results
(Steward, Perkins, & Callahan, 2014)	To examine whether depression treatment delivered before clinical CVD reduces the risk of developing CVD.	235 patients aged ≥ 60 years with major depression or dysthymia	12-month collaborative care program involving antidepressants and psychotherapy	Collaborative care for depression before CVD; 48% of the patients had a lower risk of hard CVD events.
(Dimos Mastrogiannis, 2012)	To review existing knowledge on definitions, prognosis, pathophysiological mechanism, and current and future treatment options for patients with depression and CVD, focused on heart failure.	-	A comprehensive literature review	Several pathophysiological mechanisms and behaviors linking depression and cardiac events. Improvements in medical care have prolonged survival, but it might have led to dysthymia.
(Whooley, 2006)	To evaluate the importance of major depression in patients with CVD and provide special guidance treating the disorder.	-	A comprehensive literature review	Evidence suggests that depression predicts events of CVD and antidepressant medication is associated with a decreased risk in future events.
(Glassman, O'Connor, & Califf, 2002)	To test if patients with heart failure treated with sertraline will have a lower depression score and fewer CVD.	469 patients aged ≥ 45 years with HF and depression. (234 sertraline, 235 placebo)	A randomized trial, patients took 50 to 200 mg/day of sertraline versus a matching placebo for 12 weeks	Sertraline was safe in patients with HF. However, treatment with sertraline didn't prove a greater reduction in depression and improved the risk of CVD.
(Hare, Toukhsati, Johansson, & Jaarsma, 2014)	To examine preventive strategies for depressed cardiac patients. Presents a perspective in rehabilitation and exercise programs, general support, antidepressants, and the combination of these approaches.	-	A comprehensive literature review	Evidence supports the instruction of exercise, therapies, and anti-depressants to reduced depression in CVD patients and is consistent with cardiovascular benefits.

CVD= Cardiovascular Disease; HF=Heart Failure

Table 2. Summary of preventive studies of depression and cardiac conditions.

SSRIs (selective serotonin reuptake inhibitors), SNRIs (serotonin-norepinephrine reuptake inhibitors), TCAs (tricyclic antidepressants), MAOIs (monoamine oxidase inhibitors) and antidepressants that work by other mechanisms (Rosenberg, 2014). Extensive research has been conducted to develop safe antidepressants for cardiac patients. One of the largest randomized trials in this subject is the *Sertraline Antidepressant Heart Attack Randomized Trial* (SADHART). The study was conducted with 369 participants who developed depression after a hospitalization for acute coronary syndrome. Randomly selected individuals took either an SSRI or a placebo. The results suggested that SSRIs protected the individuals by reducing platelet activation (Glassman, O'Connor, & Califf, 2002).

However, no data was found on how psychotherapy by itself affects the outcome of cardiovascular disease in patients with depression. According to our findings, no study has examined whether psychological treatment for depression reduces the risk for cardiovascular disease (Steward, Perkins, & Callahan, 2014). However, other studies have concluded that the combination of medication and psychological treatment may reduce

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anxiety, stress and depression; therefore, psychological treatment may decrease the risk of developing cardiovascular disease (Dhar & Barton, 2016).

Research on Prevention

The connection between cardiovascular disease and depression is evident. The relationship between these two conditions increases the intensity and severity of each. Evidence from observational studies demonstrates that treating depression may prevent cardiac events. A study conducted by Steward, Perkins, and Callahan focused on the treatment of depression for high-risk cardiac patients. Their results showed that treatment reduced the risk of having a chronic cardiac condition to 50%, see Table 2 (Steward, Perkins, & Callahan, 2014). Their finding indicated that treating depression reduces the risk of developing cardiovascular events, such as strokes and coronary heart disease. In addition, the data suggests that complementing recovery with a preventive depression mindset improves the cardiovascular prognosis (Rosenberg, 2014).

CONCLUSION

The bidirectional correlation between cardiovascular disease and depression should be a present concern when treating patients with one of these conditions. Preventive measures for these disorders have shown positive outcomes. Those suffering from depression have a higher risk of developing cardiovascular diseases due to the constant production of stress hormones. The constant stress and anxiety patients may experience during depression could affect the physiological mechanism of the HPA axis. These changes in the homeostatic and neuroendocrine function increase the risk of developing cardiovascular diseases. At the same time, the manifestation of depressive symptoms could affect the individual's lifestyle. If this condition is accompanied by an unbalanced diet, low physical activity, and unhealthy substance dependence, the risk of developing cardiovascular diseases increases. Further, cardiovascular conditions such as heart attacks and heart failure are usually accompanied by emotional distress. These events may increase the probability of developing depressive symptoms, which complicates the recovery process.

The combination of psychotherapy and antidepressants has shown positive outcomes by increasing quality of life. Non-medical interventions such as exercise, meditation, and breathing exercises have also been shown to increase heart and mental health. During treatment for either condition, studies suggest that having a preventive mentality can improve patients' psychological and physiological condition. To optimize patients' outcomes and prevent the comorbidity of depression and cardiovascular disease, it is important for patients to discuss mental health with their doctors. The stigma around this conversation is what causes mental illness to go undiagnosed. Further, future studies could examine if the psychological and clinical treatments for depression can decrease the probability of developing cardiovascular diseases. Understanding the comorbidity of these conditions could also encourage future clinical preventive measures that decrease the intensity of depressive symptoms and, by consequence, decrease the risk of developing cardiovascular disease.

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