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Review Article,

Depression and Cardiovascular Disease

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Abstract:
Cardiovascular diseases (CVD) are the leading cause of global morbidity and mortality. Besides imparting enormous human suffering and enhancing premature mortality, they also inflict huge direct and indirect financial costs on the worldwide society. With the easier availability of affordable therapeutics globally, and the relatively paucity of newer innovations, modifiable risk factors are gaining greater importance in the management of this cardiovascular epidemic. Depression is a modifiable risk factor. It is consistently and strongly associated with a higher risk of CVD incidence and mortality. CVD on the other hand, often induces the development of Depression. This paper reviews the effects of depression on cardiovascular diseases.

Keywords: depression, cardiovascular disease, lifestyles, mood, modifiable risk factors

Interoduction:

Major depressive disorder is diagnosed by the presence of a cluster of five symptoms, present within a 2-week period. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[1], requires that one of the symptoms should be either a depressed mood or anhedonia (loss of interest or pleasure). Secondary symptoms may be appetite or weight changes, sleep difficulties (insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to think or concentrate feelings of worthlessness or excessive guilt, and thoughts or actions of suicide.

Depression is the most common mental health disease[2]. According to the WHO, depressive disorder affects approximately 4.4% of the global population or more than 300 million people[2]. The lifetime prevalence in the general population is estimated to be 10%[3]. Women are at twice the risk of suffering from depression irrespective of their nationality, ethnicity, or culture[4]. It accounts for 3% of the global disability adjusted life years[5]. Depression co-exists with many common disorders and prognosticates a poorer course of these diseases, including premature mortality[6]. It may lead to suicide, which kills about 800 000 people globally every year[7]. Depression increases health service utilization and drives up the medical costs[8]. It is a common co-morbid disorder in patients with CVD[9].

Discussion:

CVD include coronary heart disease (CHD) high blood pressure (HTN), stroke, heart failure (HF), cardiac arrhythmias (including sudden cardiac death), peripheral arterial disease, deep vein thrombosis (DVT) erectile dysfunction (ED), or any other heart and vascular disease[10]. CVDs cause immense suffering and greatly reduce the quality of life[11]. CVDs are the leading cause of death in almost every region of the world[12]. According to the World Health Organization (WHO) 2015 statistics, CVDs account for > 17.7 million or 31% of all deaths worldwide[12].

The association between depression and CVDs is well known[13]. A recent meta-analysis of prospective epidemiological studies found that depression is associated with significant cardiovascular morbidity and mortality[14]. Many patients, however, develop depression after the CVD disease is diagnosed[15]. The result is that these conditions often coexist[16]. This co-morbidity results in higher medical costs, increased health service utilization and significant loss in productivity[17].

The underlying mechanisms are multifactorial[18]. Biological mechanisms include heightened peripheral inflammation oxidative stress, endothelial dysfunction chronic activation of the HPA axis platelet activation, and autonomic nervous system disorder with increased sympathetic activity and reduced parasympathetic activity[19-24]. Several behavioral and lifestyle factors also play a role. Depressed individuals may not maintain a healthy diet, exercise regularly, or complete cardiac rehabilitation, compared to those without depression[25-27]. They are less likely to adhere to medications or follow therapeutic recommendations[25,28]. Further, antidepressant medications may contribute to cardiovascular deleterious effects[29]. Depression screening is recommended by both the European and American Guidelines during evaluation and management of CVD patients[30]. Pharmacological and non-pharmacological intervention for depression with cardiac rehabilitation programs, exercise activity, cognitive behavior therapy appears to be beneficial in these patients[31].

Depression and HTN:

WHO estimates that, the number of people living with hypertension worldwide number 1.13 billion[32]. Its global prevalence is on the increase and is projected to rise to 29% by the year 2025[33]. Though usually silent, hypertension invariably leads to target organ damage involving the cerebrovascular, cardiovascular and the renal systems[32]. It is involved in almost 50% of CVDs and facilitates deleterious outcomes[34].

Depression is common in individuals with hypertension, affecting one in three hypertensives[35]. This incidence has been reported from all over the world, including China, USA, Africa, Spain, and Pakistan[36-40]. Its coexistence with hypertension confers greater hazard than hypertension alone for adverse cardiovascular outcomes[41]. These patients experience a poor health status and a lower quality of life[42]. They face a higher mortality rate[43]. They are often poorly compliant with treatment and have an increased utilization of medical resources[44,45].

Depression and CHD:

CHD, also known as ischemic heart disease or coronary artery disease is characterized by a diseased endothelium, low-grade inflammation, lipid accumulation, and plaque formation within the intima of the coronary arteries[46]. This may progress to stenosis, causing flow-restriction and symptomatic angina[47]. Myocardial infarction or even death may result from plaque rupture or erosion and superimposed atherothrombosis, resulting in coronary vessel occlusion[48].

Depression and CHD are frequently co-morbid[49]. The Depression Effects on Coronary Artery Disease Events (DECADE) study included a prospective cohort of 2390 patients and established depression as an independent risk factor for all-cause mortality in these patients[50]. In one meta-analysis of several prospective studies of individuals initially free of CHD, depression increased the risk of incident CHD by 30%[51]. The presence of depression in CHD patients also prognosticates poor outcomes[52]. Patients with coronary heart disease and depression have a higher incidence of chest pain and shortness of breath, higher re-hospitalization rates, and a greater risk of non-fatal cardiovascular events[53].

Depression significantly affects functionality after an MI and worsens the QOL[54]. Patients with CHD and associated depression also have significantly increased mortality[55]. A diagnosis of depressive disorder at any time after angiographically confirmed diagnosis of CAD is associated with a two- to three-fold risk of death in the following years[56,57]. Studies have shown that patients who suffer from an acute coronary syndrome also face a 2–to 2.7-fold increased risk of mortality[58]. Geulayov et al. noted an increased risk of higher mortality in depressed patients following coronary artery bypass graft surgery[59]. Depressed patients are less likely to follow lifestyle recommendations[60]. and are less compliant with treatment interventions in

Patients with CHD[61]. Depression in women, with CHD, occurs at an earlier age, is more severe, and twice as common as in men[62]. The use of antidepressant therapy and psychological support in depression patients with acute MI has been shown to reduce subsequent cardiovascular morbidity and mortality[63].

Depression and Stroke:

Stroke is the leading cause of disability and a major cause of global mortality[64]. Stroke is common - according to WHO, a patient suffers a stroke every 2 seconds, and it disables or kills a patient every 6 seconds[65]. Stroke prevalence is on the rise[66].

Depression increases stroke and worsens its prognosis[67]. In a recent analysis of 28 studies of more than 300,000 people, depressed individuals were 45% more likely to experience stroke than

those who were not depressed. Their risk of dying from stroke was also increased by 55%[68]. These ominous figures have been seen in many other studies[69-71]. The Jackson Heart Study found an almost 2-fold increase in the risk of CHD and stroke in patients with major depression[69]. The Reasons for Geographical and Racial Differences in Stroke Study also found that severe depressive symptoms were associated with an increased risk of stroke and cardiovascular mortality[70]. A recent cohort study suggested that depressive symptoms were associated with 1.4-fold risk of cardiovascular mortality[71]. Stroke survivors are also more likely depressed after a stroke[72].

Depression and Heart Failure:

HF, a chronic impairment of cardiac function usually presenting with shortness of breath, edema, and/or fatigue[73]. It affects more than 37 million individuals in the world[74]. It results in impaired functioning and poor health-related quality of life[75]. HF patients suffer from frequent hospitalizations and inflict high healthcare costs[76]. Mortality remains high despite advances in treatment, with roughly 50% of HF patients dying within 5 years of diagnosis[77].

Depression has been linked to the development and progression of HF[78]. This risk is increased by 18% to 21%diseases, after controlling for other cardiovascular risk factors[79,80]. In patients with chronic heart failure, a meta-analysis of 27 studies reported a pooled prevalence of depression of 33% in women and 26% in men[81]. Heart failure patients itself precipitates depression at a rate 2 to 3 times the normal[82]. Depression in HF patients is associated with frequent hospitalizations and recurrent cardiac events, increased health care utilization and poorer clinical outcomes, including decreased survival[83,84]. Depression further decreases the quality of life in these patients[85]. Rutledge and colleagues found that depressive symptoms or a depressive disorder in HF patients leads to a 2-fold increased risk of death[83].

Depression and Arrhythmias:

Cardiac arrhythmia is defined as any change from the normal sequence of electrical impulses[86]. Atrial fibrillation (AF) is the most common heart arrhythmia[87]. It is associated with increased morbidity and mortality[88]. It increases the risk of stroke and heart failure and imposes a significant healthcare burden[87,89].

Depression is common in AF patients[90]. Depression can shorten atrial refractory period, triggering AF and even contributing to its perpetuation[91]. Depression has been associated with an almost three-fold increase in the odds of the reoccurrence of AF after successful electric cardioversion[92]. Depression in patients with AF is associated with greater symptom severity, decreased QOL, higher mortality rates, and increased healthcare utilization[93-97]. Depression can also result from recurrent AF episodes or the development of complications such as heart failure or stroke[98]. Its occurrence increases the risk of death in these patients[99].

Individuals with depression also show an increased risk of developing ventricular arrhythmias and sudden cardiac death (SCD), both with and without concomitant CHD[100]. The World Health Organization defines SCD as a sudden unexpected death either within 1 hour of symptom onset (witnessed), or within 24 hours of having been observed alive and symptom free (unwitnessed)[101]. Two years after receiving an implantable cardioverter defibrillator, over one quarter of the patients are depressed, with the latter being higher in those experiencing more shocks[102]. Some antidepressants, used in these patients, however, may demonstrate proarrhythmic effects[103].

Depression and Valvular Diseases:

Aortic stenosis (AS) results in a hemodynamically significant narrowing of the outlet of the left ventricle[104]. On the other hand, aortic sclerosis, due to thickening or calcification of the aortic valve does not entail any left ventricular outflow tract obstruction[104]. Flow obstruction usually occur when the aortic valve area is reduced to 1 cm2 or less[105]. Severe AS is associated with mortality exceeding 50% within 2 years[106]. Treatment is usually by aortic valve replacement, either via a percutaneous or surgical approach[107].

Depression is highly prevalent in patients with aortic stenosis undergoing transcatheter aortic valve replacement and surgical aortic valve replacement (SAVR)[108]. Ho et al conducted a prospective study of 648 patients undergoing valve surgery and reported a 29% prevalence of depression preoperatively. Depression in these patients was associated with an increased mortality at 6 months post-op[109]. Oterhals et al conducted a retrospective study of 912 patients who had undergone SAVR and found that self-reported depression correlated with worse physical functioning following surgery[110]. Faria et al conducted a prospective study of 52 patients undergoing SAVR and found a 52% prevalence of depression postoperatively[111]. Depression also

increased short-term and long-term mortality in aortic valve replacement patients[112].

Congenital Heart Disease:

Congenital heart diseases (CHDs) are common types of birth defects. Each year 1.35–1.5 million children are born with CHD worldwide[113]. More than 90% of infants with CHD survive into adulthood[114].

Depression appears to be more common in ACHD compared with the general population[115]. A prenatal diagnosis of CHD in the offspring also increases maternal stress[116]. CHD appears to be more related to antidepressant use, rather than depression itself, in the pregnant women[117]. Adult survivors of CHD face several issues, including physical symptoms, lifestyle limitations and often sexual or reproductive dysfunction[118]. They have a 2- to 4-fold higher rate of depression compared to the general population[119-122]. Besides the plethora of physical stressors these individuals face, they are also uncertain about their future health and lifespan, and this further increases concomitant depression[123]. It also decreases the quality of life and increases mortality in this population[124,125].

Depression and Heart Transplant:

Heart failure patients do better with transplantation than alternative end-stage heart-failure treatments[126]. Heart transplantation in these end stage HF patients markedly improves functional status, overall quality of life and lifespan[127].

Although physical symptoms are often severe after heart transplantation, major depression in these patients is quite common[128]. It is estimated that within 5 years after heart transplantation major depression occurs in > 40% of patients[129]. This association is detrimental and results in increased morbidity and mortality in this group[130].

Depression and Peripheral Artery Disease

PA is a significant health issue globally[131]. It is diagnosed by an ankle brachial index. ABI is obtained by Doppler measurements of the systolic pressures in the lower and upper extremities[132]. An ABI <0.90 is diagnostic of PAD[133]. PAD results in significant morbidity due to claudication related restricted ambulation, lower-extremity ulcers, and commonly, a need for revascularization surgery[134]. These patients may also suffer limb loss due to amputation[135]. The decrease in the quality of life is significant[136]. Being a systemic atherosclerotic disease, it is frequently associated with an unacceptably high incidence of cardiovascular events, including new onset angina, coronary artery bypass grafting, nonfatal or fatal myocardial infarction, and congestive heart failure[137]. PAD also associated with an increase in overall all-cause and cardiac mortality[138].

The relationship between PAD and depression appears be bi-directional[139,140]. Depression is more common in patients with preexisting PAD[139] and a diagnosis of depression is associated with an increased rate of incident PAD[140]. Among patients with pre-existing PAD, depression is associated with faster progression of the disease, impaired physical function, worse revascularization patency, recurrence of symptoms after peripheral revascularization and an increased risk of major amputation[141-144]. PAD patients with depressive symptoms also experience [an] increased all-cause and cardiovascular mortality[145].

Depression and Erectile Dysfunction:

ED is the recurrent and persistent inability of having and/or maintaining a sufficient penile erection for satisfactory sexual intercourse[146]. Its etiology may be vascular, neurogenic, structural, hormonal, or psychogenic[147]. ED can also be induced by drugs or caused by trauma[148,149]. It is common and is expected to affect an estimated 322 million individuals worldwide by the year 2025150. Its prevalence increases with advancing age[151]. It reduces the quality of life in both partners[152]. It is estimated that 90% of ED cases remain untreated[153]. ED is a predictor of future cardiovascular events[154]. ED patients have comorbid depression with a frequency ranging from 8.7% to 43.1%[155,156]. Depression can itself cause psychogenic erectile dysfunction[157]. Several major studies, including meta-analytic studies have shown that not only is the incidence of ED higher in patients with depression than in those without depression, but also that depression is many times higher in patients with ED than in those without ED[158]. Depression and ED therefore appear to have a bidirectional association[159]. Further, antidepressant drugs may aggravate ED[160]. Depression further reduces the quality of life in patients with ED[161].

Depression and Venous Thromboembolism:

Deep vein thrombosis (DVT) is a common venous disease, usually involving the lower extremities[162]. Pulmonary embolism is often a consequence of DVT and is associated with significant morbidity and mortality[163]. Venous thromboembolism (VTE) is the third most common cause of vascular mortality worldwide[164]. DVT can also progress and lead to chronic complications such as the post-

thrombotic syndrome[165]. A Taiwanese study found that participants with depression had a significant 1.4-fold risk of subsequent VTE compared with those without depression[166]. In another prospective study of UK women, an association was noted with the use of anti-depressants in the previous 4 weeks prior to the development of VTE[167]. These patients had a higher risk of hospital admission and a higher mortality, when compared to women with no anti-depressant pharmacological treatment. There appeared to be no difference as to the type of antidepressant medication used.

Depression and Other CVD Risk Factors:

Depression rates are two to three times higher in people with other major CVD risk factors. These include diabetes mellitus[168], dyslipidemia[169], obesity[170], inflammation[171], and chronic renal disease[172]. Depression also lends to less compliance with healthy lifestyles. Depressed patients are more likely to engage in smoking, alcohol abuse, physical inactivity and partake in an improper diet[173].

Conclusion:

Several studies have suggested that the presence of depression doubles the risk of developing new CVD. Depression in individuals with CVD leads to poor outcomes and a higher mortality. Coexistence of CVD and depression leads to a aggravation of both physical and mental health, with an increase in morbidity and mortality rates for both. The biological mechanisms responsible for this deleterious bidirectional association are numerous. The American Heart Association and the European Society of Cardiology have labelled depression as a modifiable risk factor in CAD patients. Screening for depression is therefore essential during routine care of patients with cardiovascular diseases. Treatment of depression is therapeutically beneficial for cardiovascular outcomes. Exercise helps decrease depression and improves cardiorespiratory fitness, with better cardiovascular outcomes. Some studies have suggested that CBT is also beneficial. Pharmacological treatment for depression is also helpful in diminishing the excess CVD burden in these patients.

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