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REVIEW ARTICLE

Depression Related Pathophysiologies Relevant in Heart Disease: Insights into the Mechanism Based on Pharmacological Treatments

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Abstract: Depressive symptoms are highly prevalent in patients with cardiac diseases. Co-morbid Depression in cardiac patients causes a significant reduction in health-related quality of life for the patients and inflicts an economic burden on the society. Two types of mechanisms that may explain the link between depression and cardiac diseases are the psychosocial and physiopathological mechanisms. Physiopathological mechanisms are direct biological mechanisms, which include hyperactivity of non-adrenergic and Hypothalamic Pituitary Adrenal Axis (HPA), abnormal platelet activation, endothelial dysfunction, and inflammatory process. Psychosocial factors include behavioral or lifestyle factors like smoking alcoholism and physical inactivity. Pharmacologic and therapeutic interventions are effective at reducing symptoms of depression in patients with cardiac disorders. Among pharmacological treatment, SSRIs seems to be effective for the reduction of depressive symptoms among patients with cardiac disorders because of their good efficacy and minimal cardiovascular side effects. Mechanisms of action of SSRI's in depressive patients with cardiac disorders are associated with their ability to reduce inflammation, platelet, and endothelial dysfunction. This review focuses on the potential pathophysiological and psychosocial links between cardiac diseases and depression, the treatment options, and the importance of routine screening of depressive symptoms in cardiac settings.

Keywords: Depression, endothelial dysfunction, hypothalamic pituitary adrenal axis, inflammatory process, platelet activation, cardiac diseases.

1. INTRODUCTION

Depression and cardiac diseases are the two individual clinical disorders that are frequently co-occurring and affecting the people globally. World Health Organization Global Burden of Disease Survey indicated that heart diseases and Depression are the first and second causes of morbidity in the developed countries, which will apply to all the nations by the year 2020 [1].

The incidence rates of depressive symptoms among patients with cardiac disorders are relatively high when compared to the general population. More than half of all cardiovascular patients are under depressive symptoms. Literature suggested that approximately 17% - 27% of Out-Patients (OP) and 35% - 70% of In Patients (IP) with cardiac problems meet the criteria for depression compared to 4% - 7% in the general population. There are several modifiable and Non modifiable risks for CVDs, among which physical inactivity being one major among all the risk factors and this is highly modifiable. Depression and CVDs share these common risks to a great extent. Some more risks include high carbohydrate and fatty diets. Environment and social factors also play a key role in depression as well as in the development of CVD. Being aggravated by similar risk factors, the physiopathological relation can be predicted between CVDs and depression [2-4]. Depression is basically an adjustment disorder,r which majorly influences the patients' daily life [3, 5]. A graded relationship can be observed in patients with CVD and depression. Severe depression attack can be linked with a higher risk of cardiac morbidity and vice-versa. A probable grade model of a causal relationship can be adopted to describe the relation between depression and CVD [4, 5]. Cardiovascular induced depression is probably the form of psychological stress and similar factors. Apart from these plausible pathogenetic mechanisms, depression can also be visualized as the main driver to determine the quality of life. Literature suggests that psychosocial factors are involved in the physiological and physical pathogenesis and progression of Cardiovascular Disease (CVD) [6]. According to the American Heart Association (AHA), depressive symptoms were found to be thrice more common in post-acute myocardial infarction patients than in common

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people, which suggests a link between Depression & heart diseases [7]. Depression and the link with heart disorders are well established; these are very common and are coexisting disorders. The following sections provide a clear review of the physiopathological and psychosocial relationship between depressive symptoms and heart diseases.

2. POTENTIAL MECHANISMS LINKING DEPRESSION AND CARDIAC DISEASE

Depression is a common psychological disorder associated with Cardiovascular Diseases (CVD), which worsen the quality of life, has adverse cardiac outcomes, and increases mortality. Several pathophysiological mechanisms like inflammation, abnormal endothelial function, and disturbance in the autonomic nervous system and platelet abnormalities have been involved as a potential pathway connecting depression and heart diseases [8].

2.1. Physiopathological Mechanisms

2.1.1. Inflammation

Inflammation is an important process of development, and the progression of different cardiac disorders that occur by different mechanisms and mediators are well documented [9]. It plays a major role in destabilization and atherotic plaque rupture that leads to adverse cardio vascular events [10]. Inflammatory mediators are an important part of the pathogenesis of certain classes of Heart Diseases, especially myocardial infarction [11-14]. Inflammatory cytokines are responsible for atherosclerotic plaque formation, development, and rupture. According to various studies done, it has been identified that inflammatory cytokines (*i.e*. C-Reactive Protein (CRP) Inter Leukin-6 (IL-6) and soluble intercellular adhesion molecule 1) is the predictive inflammatory marker of cardiovascular death especially in Coronary Heart Diseases (CHD) and Heart Failure (HF) patients [15-17].

The inflammatory pathway links depression with heart diseases [18]. Inflammatory marker levels are elevated in depressive symptom patients. Elevated inflammatory cytokines levels have been associated with depressive symptoms patients with and without heart disease [19]. Patients with depressive symptoms have been found to have significantly increased inflammatory marker levels, such as C-Reactive Protein (CRP), and pro-inflammatory cytokines (IL1β, IL2, IL6), and Tumor Necrosis Factor-α (TNF- α). It has been suggested that psychological factors like negative emotions and mental stress can activate stress pathways resulting in acceleration of inflammatory, which can lead to the progression of adverse cardiac outcomes in patients with depressive disorders *via* atherosclerosis [20].

2.1.2. Endothelial Dysfunction

Endothelial dysfunction is a fundamental element of heart disease, especially Acute Coronary Syndrome. Normal endothelium produces nitric oxide in response to serotonin, that results in vasodilatation. The atherosclerotic artery fails to do so, leading to vasoconstriction and subsequent platelet aggregation. Endothelial dysfunction is a condition in which "The partial or complete loss of balance between vasoconstrictors and vasodilators, growth-promoting and growth-inhibiting factors, proatherogenic and antiatherogenic factors" [21]. It is the initial stage in the development and progression of atherosclerosis and is involved in plaque progression, increased platelet aggregation, and decreased production of anti-inflammatory factors [22]. It is also associated with an impairment of dilation of blood vessels characterized by mitigation of nitric oxide level, and an increase in endothelial-derived contracting factors. Endothelial function is quantified by flow-mediated dilation of the brachial artery [23].

Sherwood *et al*. reported that depressive patients with heart diseases had an endothelial dysfunction when compared with non-depressed heart disease patients, which indicated the role of the endothelium in the pathogenesis of depression and heart diseases. To confirm this correlation, literature provides evidence that Selective Serotonin Reuptake Inhibitors (SSRIs) promote endothelial function in cardiac and depressive patients suggesting that, when endothelial dysfunction is linked with depressive symptoms in patients with heart diseases [24-27].

2.1.3. Platelet Activation and Aggregation

Platelet plays a vital role in thrombogenesis by interaction with endothelial components and coagulation factors. Activated platelets trigger plaque and thrombus formations, which are the major pathophysiological processes involved in various cardiovascular disorders. In atherosclerotic arteries, serotonin mediates platelet aggregation by binding with 5 Hydroxy Tryptamine (5-HT). Elevated serotonin levels are the predictors of future ischemic cardiac events in patients with suspected CAD [28]. Literature suggested that depressed patients have an abnormal level of blood platelet serotonin levels, decreased platelet serotonin transporter levels, and increased platelet serotonin receptor concentrations [29]. Serotonin, an endogenous substance is mainly involved in the pathogenesis of depression, which binds to 5-Hydroxy Tryptamine (5-HT) receptors on platelets, hence plays a major role in platelet biology [30].

The catecholamines bind with alpha 2a receptors on platelets and results in degranulation of alpha and beta granules. Degranulation of alpha granules of platelet causes the release of platelet activation markers and proinflammatory cytokines. Confirming this, it has been observed that platelet activation marker levels (Platelet Factor-4 (PF-4) and beta Thrombo Globulin (βTG)) are higher in depressed patients with cardiac disorder than in nondepressed cardiac patients and controls. This evidence confirms that patients with depressive symptoms have hyperactive platelets and are removed from the bloodstream to an extent. These evidences indicate the key role of platelet dysfunction in the pathogenesis of heart and depressive disorders. Several clinical studies have identified that SSRI's diminishes the risk of thrombotic events by serotonin and collagen mediated platelet aggregation. Reuptake inhibitors increase the extracellular neurotransmitter levels by limiting their reabsorption and reuptake. So these medications are safe for heart disease patients with depressive symptoms [31, 32].

2.1.4. Neurohormonal and Autonomic Nervous System Dysfunction

Neurohormonal activation links depression and heart disease. A higher concentration of catecholamines (epinephrine and norepinephrine) has been observed in cardiac patients as a result of sympathoadrenal activation [33]. The activation of the sympathoadrenal system can accelerate vasoconstriction, hypertension, rapid heart rate, and platelet activation in cardiac disease patients. It has been shown that in depressed coronary heart disease patients, there is an elevated level of norepinephine and cortisol in the blood and cerebrospinal fluid. This may be due to an alteration of the autonomic nervous system leading to increased mortality in these patients [34]. HPA-related abnormalities result in the development and progression of other clinical conditions like metabolic disorders such as obesity, hypertension, glucose intolerance, hypertriglyceridemia, and hypercholesterolemia, which are directly responsible for adverse cardiovascular outcomes.

Dysfunctioning of catecholamines and autonomic nervous system abnormalities also links the relation between depression and cardiac disorders. The cardiac system is innervated by the parasympathetic and sympathetic nervous systems; the action between these two opposing forces aids the cardiac system to make alterations in reaction to stressors [35]. Studies suggest that patients with depressive symptoms show activation of the sympathetic system in response to acute stressors. Increased sympathetic and decreased parasympathetic activity in patients with cardiac disorders especially patients who are diagnosed with Ischemic Heart Diseases (IHD) and Heart Failure (HF), is characterized by reduced baroreflex sensitivity and decreased Heart Rate Variability (HRV). The imbalance between sympathetic and parasympathetic nervous systems leads to the lack of Variability in the Heart (HRV) and Heart Rate (HR) [36].

HRV is considered as a marker of ANS dysfunction. Studies identified that depressed patients had reduced HRV. The reduction shows a linear relationship with the severity of depressive symptoms. More severe depressive symptoms shows a significant decline of HRV. Moreover, depressive patients with cardiac disorders have a significant reduction of HRV compared to patients with depression or cardiac disease alone. Carney *et al*. found that depressed cardiac patients had less HRV than non-depressed heart disease patients. This indicated that the outcomes of heart and depressive disorders on HRV are additive. HRV decreases as a result of increased autonomic dysfunction that leads to arrhythmia and adverse cardiac outcomes in depressive patients with cardiac disorders [37, 38]. Table **1** shows a summary of clinical studies that evaluate the pathway linking depressive symptoms in cardiac patients.

Table 1. Summary of epidemiological studies that evaluate the mechanisms link between Depressive symptoms in cardiac patients.

Authors and Year	Mechanism	Objective	Observed Markers	Findings
Hekler *et al*. [39], 2007	Inflammation	To determine whether inflammatory markers in MI patients are prospectively associated with depressive symptomatology.	IL-6 and IL-1b.	Bivariate and multiple regression analyses revealed a significant positive prospective association between baseline IL-6 and depressive symptoms 7 months later.
Smith *et al*. [40], 2007	Inflammation	To investigate the impact of depression and inflammato ry markers assessed 2 months after ACS, on MACE's over 2 years.	CRP, IL-6 & SIAM	C-RP levels were also associated with increased MACE risk. C-reactive protein levels and BDI-II scores interacted in predicting MACEs.
Shimbo *et al*. [41], 2006	Inflammation	To examine the relation between the course of depression and CRP concentrations after an ACS.	CRP	Depressed patients were more likely to have raised CRP concentrations than were the persistently nondepressed group. Compared with the remittently depressed patients, the persistently nondepressed group also were less likely to have raised CRP concentrations, although this difference was not significant. CRP concentrations did not differ significantly between the remittently and persistently depressed patients.
Drago *et al*. [42], 2007	Influence on ANS	To determine whether depressed patients present a cardiac autonomic dysfunction and whether this could represent the mediator of the influence of depression on their prognosis.	HRV	Patients with MDD showed lower HRV and higher HR than patients without MDD; moreover mild to moderate symptoms of depression were associated with lower HRV but not with significantly higher HR.
Carney *et al*. [43], 1995	Influence on ANS	This study tests the hypothesis that depressed patients with CAD have decreased HRV compared with nondepressed CAD patients.	HRV	HRV was significantly lower in depressed than nondepressed patients, even after adjusting for relevant covariates. Thus, decreased HR variability may help explain the increased risk for cardiac mortality and morbidity in depressed CAD patients.
Thode *et al*. [44], 1997	Abnormal platelet activation	This study investigated the hypothesis that patients suffering from IHD and depression concurrently may have abnormal platelet activation resulting in an increased risk of thrombosis.	PF4 and beta-TG	Mean PF4 and beta-TG plasma levels in the IHD group with depression were found to be significantly higher than those of the control and IHD groups.
Sherwood *et al*. [24], 2005	Endothelial Dysfunction	The purpose of this study was to assess whether depressive symptomatology was associated with vascular endothelial dysfunction in patients with coronary heart disease.	FMD of the brachial artery	Patients with significant depressive symptomatology, as indicated by BDI showed attenuated FMD compared with patients that were not depressed. The use of antidepressant medication was associated with improved FMD.

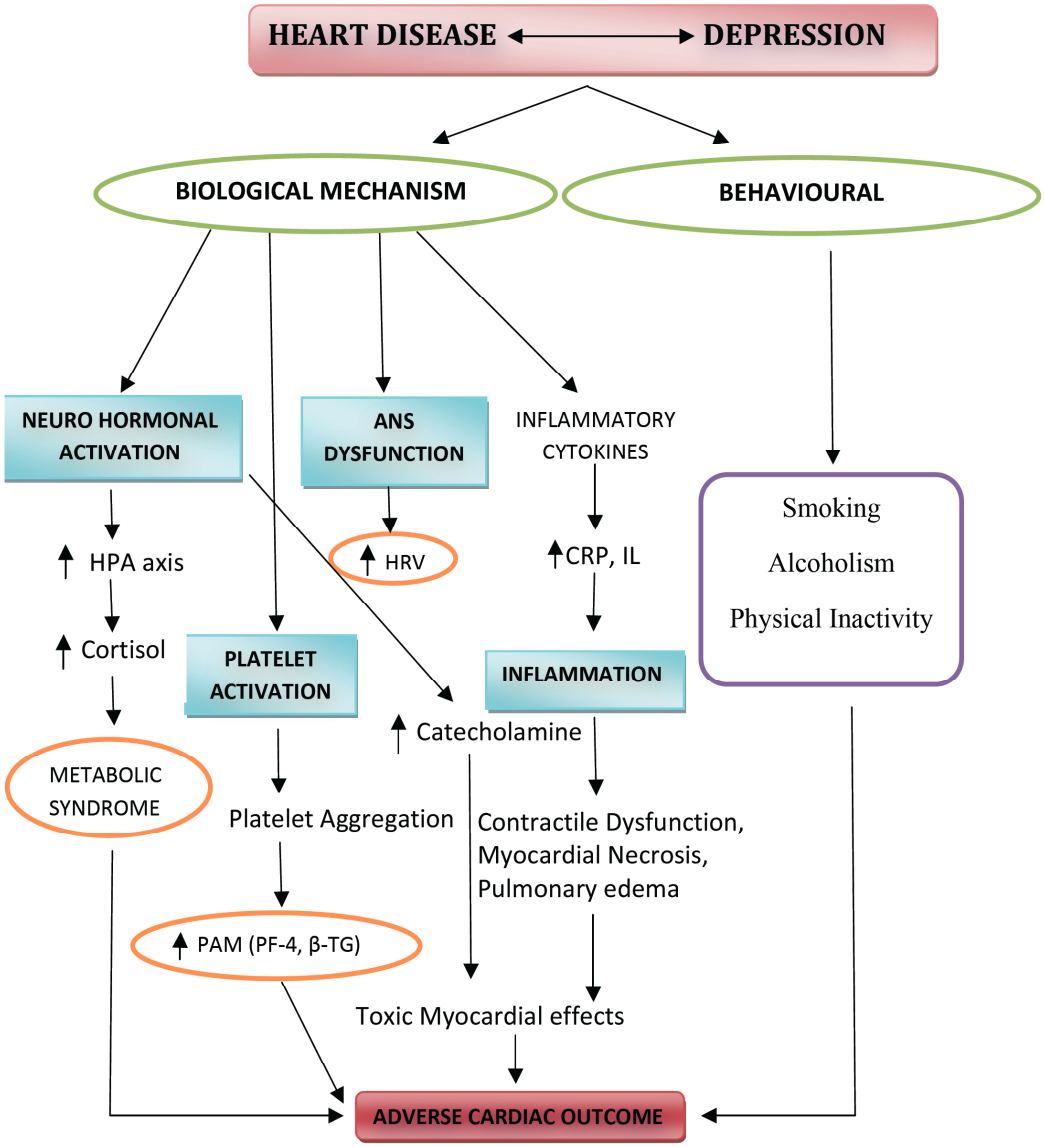

Fig. (1). Schematic representation of potential mechanisms explain the relation between depression Heart disease and adverse cardiac outcomes. IL-6- Inter Leukin-6, CRP- C-reactive protein, HRV- Heart Rate Variability, PF4- Platelet Factor, β-TG- Beta Thrombo Globulin, ANS: Autonomic Nervous System, PAM-Platelet Activating Marker. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

2.2. Psychosocial Mechanism

2.2.1. Behavioral Factors

Several behavioral factors are involved in the pathway linking heart depressive disorders. Patients with depressive symptoms are unlikely to engage in health improvement programmes, including regular exercise, adhere less to medications, maintenance of balanced diet, ceasing to smoke, and incomplete cardiac rehabilitation programs [45]. All these psychosocial factors may significantly associate with an adverse cardiac outcome in certain populations with depression. Several studies confirm that the introduction of exercise, talking therapies, and changes in life style factors can reduce depressive symptoms in cardiac patients [46]. Potential pathophysiological mechanisms explaining the relationship between depression, heart disease, and the adverse cardiac outcomes are shown in Fig. (**1**).

3. TREATMENT OF DEPRESSION IN CARDIAC PATIENTS

3.1. Pharmacological Interventions

Several pharmaceutical therapies have been studied in depressive cardiac patients. Tri Cyclic Antidepressants (TCAs) acts by enhancing serotonin, nor epinephrine, and dopamine levels in the brain. Although these medications are useful in reducing depressive symptoms but they are suboptimal in cardiac patients because of some limitations in their efficacy [47]. Antagonism of muscarinic acetylcholine receptors, histamine receptors and alpha-1 adrenergic receptor causes anticholinergic, cardiovascular and neurological side effects [48]. Major cardiovascular side effects are tachycardia, arrhythmia, ECG changes and orthostatic hypotension especially in patients with ischemic heart diseases, which leads to sudden cardiac death [49]. In fact, these

first-generation antidepressants have been significantly linked with more cardiovascular side effects in patients with cardiac diseases, and they and need to be replaced if safer treatment options are available [50]. Despite the first generation TCAs, SSRIs appear to be more safe and efficacious in cardiac patients as they have very less or no affinity to histaminic muscarinic and alpha receptors [51]. Their relative safety and better acceptability have made them first-line drugs in depressive patients with heart diseases. Results from multicenter clinical studies support the effectiveness of SSRI's in depressive symptoms patients with comorbid cardiac disorders [52].

3.2 Non-Pharmacological Interventions

Recent evidence directed toward the various management modalities ranging from cardiac rehabilitation, cardiac exercise and training showed improvement in psycho neurological functioning, thus reducing all-cause mortality [53]. This is well understood that regular physical exercise prevents the incidence of depression in cardiovascular patients. Regular mild to moderate physical exercise for a duration of approximately 150 minute weeks may significantly reduce the cardiovascular events and simultaneously contribute to patient wellbeing by protecting depressive and other psychoneurological disorders [54, 55]. This complex medical condition can be prevented by cardiac rehabilitation therapies. Depression treatment in post-MI patients improves their quality of life and perhaps long-term cardiac outcomes. The attitude of patients also contribute significantly to the patients' health outcome. Hence, continuous and high levels of motivation are required for these types of patients for regular physical exercise and cardiac rehabilitation therapy [56].

CONCLUSION

Depressive and cardiac symptoms are similar, which makes them challenging to differentiate between each other. American Heart Association (AHA) also recommended screening for depression in patients with established CHD. The same recommendation was made by various other scientific studies where they suggested for mandatory screening of cardiovascular patients for neuropsychiatric disorders. In addition to having a clear insight into this condition, the proactive approach to address the psychological and social function also seems to have equal importance. Several pieces of evidence have been drawn in current scientific studies on antidepressive therapies. These also hint the same findings, yet more studies should be carried out to reach conclusive evidence. A better understanding of pathophysiological mechanisms is one of the basis for understanding the complex biological processes taking place in co-morbid conditions. Untying of such biological complexities is the basis for framing policies and future therapeutic strategies. Screening of depressive symptoms in cardiac settings helps to identify patients who may require further stratification and therapy. Hence, health care professionals should carry out routine screening methods to differentiate depressive symptoms for those diagnosed with cardiac disorders. Thus, effective screening and proper management can reduce mortality and adverse cardiac outcomes in patients with cardiac disorders.

LIST OF ABBREVIATIONS

AHA	=	American Heart Association
ANS	=	Autonomic Nervous System
CRP	=	C-reactive protein
HPA	=	Hypothalamic Pituitary Adrenal
HRV	=	Heart Rate Variability
IL-6	=	Inter Leukin-6
IP	=	In-patients
OP	=	Outpatient
PAM	=	Platelet Activating Marker.
PF4	=	Platelet Factor
β-TG	=	Beta Thrombo Globulin

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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