

Review Article

The Interface of Coronary Artery Disease and Depression: Pathophysiology and Diagnosis

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Coronary Artery Disease (CAD) and depression are two of the most common human health problems. The association between CAD and depression is suggested to be bidirectional: depression is highly prevalent among patients with CAD and depression behaves as a risk factor for the development of CAD. Both diseases are complex disorders that are influenced by genetic and environmental factors. It has been suggested that depression is associated with both physiological and psychosocial changes that are deleterious to the cardiovascular system; although, the mechanisms underlying this connection remain unclear. There is a large body of literature demonstrating that pro-inflammatory cytokines, endocrine factors, and metabolic markers contribute to the pathophysiology of depressive disorders and antidepressant response. Although, it has been suggested that sex differences in the prevalence of major depression among cardiac patients exist: the prevalence of major depression is approximately two-times greater in women with CAD compared to men, similar to the general population. Depression is under-recognized in CAD patients because healthcare providers rarely use standardized screening instruments. For this reason, it is important to have a systematic screening for depression in all CAD patients.

The aim of the present review was to systematically report current evidence on the biological mechanism at the base of depression-CAD relationship and the diagnostic method available in CAD patients.

Keywords: Coronary Artery Disease; Depression; Plasma Biomarkers; Life style

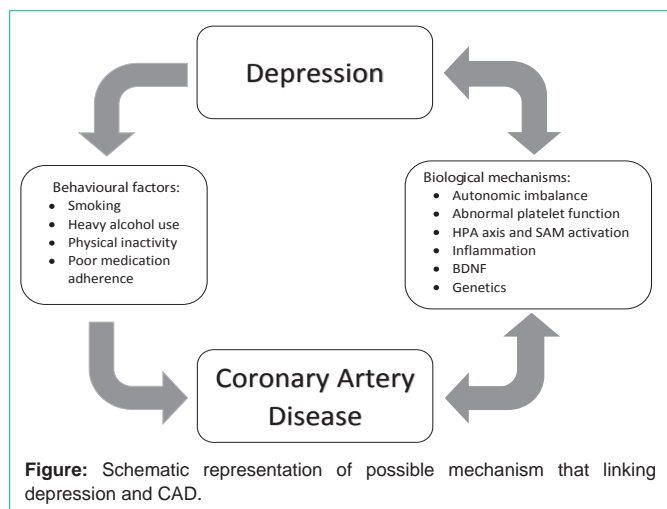
Introduction

Depression and Coronary Artery Disease (CAD) are both extremely prevalent diseases that compromised quality of life and life expectancy. It is well known that depression is highly prevalent among patients with CAD [1] and depression behaves as a risk factor for the development of CAD [2,3]. For this reason, the relationship between depression and CAD has been proposed to be bidirectional. Many prospective and retrospective studies have investigated the association of existing depression and CAD founding a significant positive correlation with a moderate effect size of 1.5–2.7 [4–6]. In addition, several studies have investigated the role of depression status as a prognostic factor in patients with existing CAD, suggesting that depressed patients have a 1.6–2.7-fold increased risk for further cardiovascular events within 24 months [7,8]. In patients with cardiovascular disease, the prevalence of major depression ranges around 15–20% [9], and the prevalence of elevated depression symptoms have been reported to be as high as 50% [10]. In particular, in patients with acute myocardial infarction, major depression was identified in 19.8% [1]. The presence of a depressive episode in CAD patients is associated with an elevated risk of secondary acute ischemic events, poorer compliance with risk factor interventions, and increased mortality independently of traditional cardiac risk factors [11,8].

Pathway linking depression and CAD

Established coronary risk factors such as hypercholesterolemia, hypertension, diabetes, obesity, and smoking are bound to accumulate in depressed patients [12]. A number of reasonable bio behavioral mechanisms are suggested to underlie the relationship between depression and CAD: treatment adherence and lifestyle factors such as smoking, heavy alcohol use, and physical inactivity. Depression is associated with an unhealthy lifestyle, such as decreased adherence to dietary and exercise regimens, increased alcohol intake and rates of smoking [13,14]. For these reasons, it has been suggested that depression is associated with both physiological and psychosocial changes that are deleterious to the cardiovascular system; although, the mechanisms underlying this connection remain unclear [15]. Depression is also associated with physiopathological changes that negatively influence the cardiovascular system, among which nervous system activations, cardiac rhythm disturbances, multi distrectual inflammation, and hypercoagulability (Figure).

The evidence of less Heart Rate Variability (HRV) in CAD patients with depression than non-depressed cardiac patients [16] may explain the possible role of autonomic imbalance in depression and CAD. Absence of HRV realizes a sympathetic-vagal disparity and is a risk factor for ventricular arrhythmias and sudden cardiac death in patients with cardiovascular disease [17]. This is aggravated among depressed patients with myocardial infarction, suggesting that low



heart rate variability may facilitate the adverse outcome of depression on survival after a myocardial infarction.

Abnormal platelet function has been identified as possible links between depression and CAD. The role of platelets in atherosclerosis, thrombosis and acute coronary syndromes is well known. In addition, it was demonstrated that plasma levels of platelet factor IV and beta-thromboglobulin, markers of platelet activation, are higher in depressed patients with ischemic heart disease than in non-depressed patients with ischemic heart disease and control patients [18]. Interestingly, in depressed patients with myocardial infarction, treatment with a selective serotonin reuptake inhibitor, the sertraline, cause less activation of platelets and endothelial cells [19].

Biological mechanisms that might link these two conditions together include the Hypothalamic–Pituitary–Adrenal (HPA) axis and Sympathetic Adrenal Medullary (SAM) activation. This contribution may be mediated by the loss of glucocorticoid receptor-mediated negative feedback on inflammatory signaling. It is also worth noting that the disruptions of the HPA axis may be reciprocally regulated by altered expression of pro-inflammatory cytokines constituting a complex bidirectional biological crosstalk [20]. Dysregulation of the HPA axis may also lead to sympathoadrenal hyperactivity via central pathways. Sympathoadrenal activation leads to catecholamine production and subsequent tachycardia, vasoconstriction, and platelet activation [21].

The contribution of inflammation to the overall development of cardiac disease is well documented. Inflammation plays a key role in the initiation and promotion of atherosclerosis and may lead to Acute Coronary Syndrome by induction of plaque instability. For this reason, numerous inflammatory markers have been extensively investigated as potential candidates for the enhancement of cardiovascular risk assessment [22].

Some studies investigating also immune system functioning in subjects with depression and found high levels of inflammatory markers, particularly C-reactive protein and cytokines (interleukin-6 (IL-6), interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α)), in individuals with depression [23,24]. Since vagal tone inhibits the secretion of inflammatory cytokines, treatments that stimulate the vagus nerve such as exercise, biofeedback, and meditation may

have favorable anti-inflammatory consequences [25]. Peripheral concentrations of inflammatory biomarkers, vascular endothelial dysfunction, and heightened platelet reactivity may be important processes that contribute to depression in CAD patients [26]. It is thought that repeated or prolonged activity of inflammatory processes and related pathophysiology can contribute to the persistence of depressive episodes and lead to neurodegeneration [27]. The pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) have direct inhibitory effects on adult hippocampal neurogenesis [28,29]. Cytokines include a number of pleiotropic proteins that have been extensively implicated in the process of inflammation. One of the major subset of mediator contributing in the interaction between inflammatory cells and endothelial and smooth muscle cells and the subsequent perpetuation of the inflammatory reaction are cytokines, especially the interleukins, and macrophage-associated cytokines like tumor necrosis factor (TNF)- α and interferon (IFN)- γ . Their serum levels correlate positively with occurrence and severity of CAD, underlining their central role in the pathogenesis of atherosclerosis [30].

A large number of clinical studies have reported that Brain Derived Neurotrophic Factor (BDNF) plasma and serum levels are significantly decreased in depressed patients, and that this decrease is normalized by antidepressant treatments [31-33]. These findings suggest that blood BDNF may be a useful biomarker for depression and that it could have a potential role in the pathophysiology and treatment of mood disorders. In fact, BDNF plays a critical role in regulating both vascular development and response to injury, and promotes survival, differentiation, and maintenance of neurons in peripheral and nervous system [34]. BDNF is also expressed in atherosclerotic coronary arteries [35] suggesting its possible role in the pathogenesis of CAD. The precise role of BDNF in the pathogenesis of CAD is not clear but appears to be associated with an increased inflammatory response by activated T cells and macrophages in atherosclerotic coronary arteries [36]. A previous work by Bozzini S et al. (2009) was aimed to study the possible correlation between the Val66Met polymorphisms in BDNF gene and depression in CAD patients [37]. They showed the possible involvement of the AA genotype and in the predisposition to CAD associated with depression. This polymorphism has been found to be associated with neuropsychiatric disorders including Alzheimer's disease, Parkinson's disease, depression, and bipolar disorder [38-41]. Humans carrying the Met allele have smaller hippocampal volumes and perform poorly on hippocampal dependent memory tasks [42,43]. It has previously been shown that Met variant alters the intracellular trafficking and activity-dependent secretion of BDNF in neurosecretory cells and neurons [42,44].

Pharmacogenomic studies have evaluated the moderating effect of specific genetic variation on response to antidepressant therapies and Single-Nucleotide Polymorphisms (SNPs) in several genes was found to be associated with response or adverse effects with antidepressant [45]. These included, among others, 5-hydroxytryptamine and the serotonin transporter (SLC6A4) long/short variants. Evidences suggest that BDNF can enhance serotonergic transmission that modulates different brain functions and it is known to regulate sleep, appetite, pain, and inflammation [46]. The complex serotonin (5-HT) neuronal system is under a bottleneck control by a single protein, 5-HT transporter (5-HTT). By controlling reuptake of

5-HT from the extracellular space, 5-HTT regulates the duration and strength of the interactions between 5-HT and its receptors. A polymorphism within the 5-HTT 5' upstream region (5-HTTLPR) has been reported, the majority of which is composed of either 14 (S) or 16 (L) repetitive elements. In humans, although infrequent, 18 and 20 repetitive elements (XL) are also present [47-50]. An *in vitro* transcriptional assay indicated that the activity of the human 5-HTT promoter is regulated by these polymorphic repetitive elements, resulting in differences in the efficacy of 5-HTT reuptake among the allelic variants [51]. It previously observed a significant increase of L/L genotype and a decrease of S/L genotype respect to controls and a greater frequency of L allele, responsible for enhancing the efficiency of transcription, in CAD patients. These results may be responsible of the increased capacity of platelet serotonin uptake previously observed in patients with CAD [37].

Diagnosis of depression in CAD patients

Depression is under-recognized in CAD patients because healthcare providers rarely use standardized screening instruments [52-54]. The American Heart Association (AHA) recommends systematic screening for depression in all CAD patients using the Patients Health Questionnaire-2 (PHQ-2) [55], which was approved by the American Psychiatric Association. It has been shown that 20% of patients with recent myocardial infarction meet the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for major depression and score higher on depressive manifestations [56]. For the identification of depressed subjects, there are several questionnaires. The Patient Health Questionnaire (PHQ-2) provides two queries that are suggested to identify depressed patients [57]. If the answer is "yes" to one or both questions, it is recommended PHQ-9, a screening tool of depression concise, containing nine questions, to which most of the patients are able to respond fully without assistance [The MacArthur Initiative on Depression and Primary Care. Patient health questionnaire tool kit for clinicians. Available from:]. It provides a conditional diagnosis of depression as well as the layering of gravity, which is useful for the choice of treatment and monitoring.

The Hospital Anxiety and Depression Scale (HADS) [58] was shown to be a reliable depression screening instrument in general practice and in medical patients, but yielded conflicting results in CAD patients [59,60]. In CAD patients, the Beck Depression Inventory-II (BDI-II) [61] is widely used, but there are a few studies evaluating the psychometric properties of the BDI-II in stable CAD patients [62,63]. In 2011, Bunevicius A et al. evaluated the internal consistency and psychometric properties of the HADS and the BDI-II for screening of major depressive episodes in CAD patients undergoing rehabilitation. They found that internal consistencies of the HADS and BDI-II are high. The BDI-II and HADS-A demonstrate the higher sensitivity compared to the HADS-D and HADS-total for screening of major depressive episodes in CAD patients. Positive predictive values for the BDI-II and for the HADS were low indicating that a large proportion of patients with positive screening results did not meet criteria for major depressive episodes [64].

Gender studies

Women have traditionally received less focus in heart disease research relative to men, despite well-known gender differences indicating comparative less aggressive treatments, less accurate

diagnostic tests, and higher post-myocardial infarction mortality among women [65,66]. Depression rates among women exceeded for men by factor of more than 2 to 1 [67] and they may be associated with clinical symptoms that affect cardiac diagnosis and treatment [65]. Biological factors such as hormones and psychosocial factors such as role overload have been postulated to explain this gender difference [68]. Although it has been suggested that sex differences in the prevalence of major depression among cardiac patients exist [69]. A meta-analysis performed by Shanmugasagaram S et al., in 2012 demonstrated that the prevalence of major depression is approximately two-times greater in women with CAD compared to men, similar to the general population [70].

Conclusion

Clinical and preclinical studies have identified a number of factors that may serve as putative biomarkers for diagnosing and treating depression in CAD. However, the utility of any given growth factor, cytokine, endocrine factor, or metabolic marker to serve as a clinically useful biomarker is limited by a lack of sensitivity and specificity. A number of behavioral mechanisms were suggested to underlie the relationship between depression and CAD: treatment adherence and lifestyle factors such as smoking, heavy alcohol use, and physical inactivity. Depression foresees reduced adherence to prescribed regimens and it is also related with increased alcohol intake and physical inactivity, with increased rates of smoking and may lower the success of smoking cessation programs in CAD patients.

Similar to the general population, the prevalence of major depression is approximately two-times greater in women with CAD compared to men. Given the poorer prognosis associated with comorbid major depression in CAD it is important to devote more attention to identify and address potential factors that could account for gender differences in depression. CAD-related mortality in women is high and the prevalence of depression among women in the general population is big. Guidelines require screening of depression in patients with ischemic heart disease, from which women could benefit, stressing the need to systematically assess the presence or absence of a gender gap in depression.

As the link between depression and CAD has become increasingly predictable and established between specialists, pharmacologic and no pharmacologic interventions on depression in patients with heart disease have come into practice. Therapeutic advances have shown a persuasive link between successful management of depression in patients with CAD and a reduction of cardiovascular events. However, the investigations addressing this hypothesis have demonstrated a variety of conclusions. Some mechanisms were proposed to explain antidepressant toxicity, such as ventricular arrhythmias from prolonged QTc, vasoconstriction from serotonin and bleeding to platelet inhibition from Selective Serotonin Reuptake inhibitors (SSRI). Other studies indicate mood and cardiac prognosis improvement in persistent depression among post-acute coronary syndrome patients by antidepressant and/or psychotherapy. However, the literature does not indicate clear superiority of any particular psychotherapy and the treatment response and medical prognosis of different patients' subgroups appear heterogeneous [71].

Depressive symptoms and CAD are both associated with

increased inflammation and exercise intervention have been shown to reduce inflammation in these patients with a significant reduction in morbidity and mortality [72,73]. Some studies reported that physical activity plays a particularly important role in reduction the risk of cardiovascular events among CAD patients with depressive symptoms [74]. However, CAD patients with depressive symptoms are less prone to increase physical activity over 12 month compared with those without depressive symptoms [75]. Of note, increased physical activity may ameliorate depressive symptoms; by itself, an intensive 16-week aerobic exercise regimen has shown to be as effective as pharmacologic therapy in treating older adults for major depressive disorder [76].

Depressive symptoms should be seen by the cardiologist emerging risk factor for cardiovascular disease, and as such, its early detection through simple questionnaires should more lead to a long-term lifestyle change, as well as a therapeutic treatment.

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