Depression and Cardiovascular Diseases

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Abstract

Cardiovascular diseases (CVD) and depression share a common epidemiology, thus suggesting a mutual link between these two disorders. Growing evidence supports the detrimental influence of depression on cardiovascular risk factors and outcomes. Reciprocally, depression rates in patients with known CVD are higher than in the general population. Heart and brain seem to be intertwined in a psycho-neuro-hormonal-cardiovascular axis. Their disorders emerge from pathophysiological derangements in the same fundamental mechanisms, including inflammation, platelet reactivity, autonomic dysregulation, circadian rhythm and sleep disruption, hormone imbalance, and neurotrophins. In addition, common unhealthy lifestyle habits, mainly poor diet, low physical activity, and tobacco use, might

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help explain the association between depression and CVD. Notwithstanding this, depression is grossly under-detected and undertreated in patients with CVD. The application of pharmacological and nonpharmacological approaches to the treatment of depression might help physicians to optimize health outcomes and quality of life for their CVD patients.

Keywords

Inflammation · Platelet reactivity · Endothelial dysfunction · Autonomic imbalance · Circadian rhythm · Renin-angiotensin-aldosterone system · Vasopressin · Hypothalamic-pituitary-adrenal axis · Neurotrophins · Antidepressants

Introduction

Cardiovascular diseases (CVD) refers to those conditions that affect the heart and blood vessels, including coronary heart disease, cerebrovascular disease, and peripheral artery disease. CVD is the primary cause of mortality and is considered one of the highest economic costs in many countries. In a recent report, the American Heart Association estimated that medical costs and productivity losses of CVD are expected to grow from $555 billion in 2015 to $1.1 trillion in 2035. In many developing countries, mortality and morbidity from CVD have increased exponentially. It is estimated that in 2008 about 7.3 million global deaths resulted from CVD, which account for one in every six deaths. There were significant differences by sex, age, ethnicity, and geographic region in the proportion of persons who had been diagnosed with CVD. Men were more likely than women to be diagnosed with CVD. Non-Hispanic whites were more likely than any other ethnic groups to be diagnosed with CVD (39.1%). Physical activity, healthy diet, and lifestyle are probably the most crucial ways to prevent CVD.

Depression is a common mental disease. It is estimated that major depressive episodes have a prevalence of 14.6% in high-income countries and 11.1% in developing countries. Depression became the second leading cause of disability in 2010. According to current international classifications (International classification of disease, ICD-10 and diagnostic and statistical manual of mental disorders, DSM 5), a major depressive episode is defined by five or more of the following nine symptoms lasting for at least 2 weeks nearly every day. One of these symptoms must be depressed mood or anhedonia (loss of interest in activities or pleasure). Other symptoms are: significant decrease or increase in weight or appetite; insomnia or hypersomnia, fatigue, psychomotor agitation, or retardation; diminished ability to concentrate or make decisions; feelings of worthlessness or inappropriate guilt; and recurrent thoughts of death or suicidal ideation. Depressive symptoms and major depressive episodes are among the building blocks of "Mood disorders," a chapter of the previous editions of the DSM, which has been split into "Depressive disorders" and "Bipolar and related disorders" in the DSM 5. It is beyond the scope of this chapter to provide a detailed description of the diagnostic criteria for depressive and bipolar disorders. Briefly, a diagnosis of major depressive disorder (MDD) can be made in presence of one or more major depressive episodes, with no lifetime (hypo)manic episodes. Nonetheless, a major depressive episode is often the first presentation of bipolar disorders, and it is not rare that an initial diagnosis of MDD transitions to bipolar disorder. Also, depressive presentations not reaching the diagnostic threshold for a major depressive episode in terms of either duration or symptom count may be present in other depressive (persistent depressive disorder, disruptive mood dysregulation disorder, premenstrual dysphoric disorder) or bipolar (cyclothymic disorder, other specified bipolar and related disorders) disorders. In this chapter we will mainly refer to depression as a psychopathological dimension. When data is presented which is relevant for a specific diagnostic category, this will be specified.

Biological and psychosocial factors contribute to the emergence of depression, especially in the elderly. Genetic vulnerability may make some people more susceptible to depression. Among

biological risk factors are old age and female sex. In the elderly, according to the so-called "vascular depression" hypothesis, depression has been linked to vascular brain lesions, chronic inflammation, and atherosclerosis, which is also the leading cause of CVD. Similarly to CVD, poor lifestyle habits, such as smoking and alcohol use, are important risk factors for depression, especially in the elderly. Some authors suggest that depression could be prevented by improving lifestyle habits, such as exercise, diet, smoking cessation. Furthermore, treatment for hypertension, hypercholesterolemia, and hyperglycemia, conditions traditionally related to CVD, could ameliorate depression as well.

In the present chapter, we will review the pathophysiological mechanisms underlying the interaction between CVD and depression. We hope to convince physicians of the uttermost importance of monitoring the cardiovascular state of depressed patients and, reciprocally, assessing the mood profile in patients suffering from CVD. Also, a more thorough understanding of this association could help developing novel lines of interventions.

The Reciprocal Association Between Depression and CVD

Evidence accumulated of a reciprocal association between depression and CVD. Psychosocial risk factors, including depression and anxiety, have been found to be strongly and consistently correlated to a worse outcome of CVD [1]. On the other hand, CVD can increase the risk of developing depressive symptoms and disorders through either biological, bodily, or psychosocial changes. In fact, the association between depression and CVD can be considered a downward spiral in which depression and CVD reinforce each other [2]. Incidence rates of depression in patients with CVD reach up to 20–40% [3]. Reciprocally, depression increases the risk of cardiac death by 3–4 times [4]. Depression and anxiety are common symptoms among patients who have suffered an acute cardiac event and sometimes can persist for months or even for years, influencing patients' quality of life [5]. Moreover, depression may lead to complications, as depressed patients have a reduced pharmacological compliance and have more difficulty coping with the distress of a disease [4]. In summary, depression has a major impact on mortality, morbidity, and functional recovery in patients with CVD.

The socio-psycho-biological model of modern medicine suggests that CVD may be viewed as a part of a psycho-neuro-hormonal-cardiovascular axis, which links the brain and the heart. Several biological mechanisms might be involved, including inflammation, platelet reactivity, autonomic dysregulation, circadian rhythm and sleep disruption, hormone imbalance, neurotrophins, lifestyle, and metabolic syndrome.

Inflammation

Atherosclerosis is a chronic inflammatory disease, orchestrated by endothelial and white blood cells through numerous cytokines. Chronic inflammation in CVD results from an oxidative/anti-oxidative imbalance, which determines an accumulation of oxidized low-density lipoproteins (LDL) in the arterial wall. This generates an inflammatory response in the subendothelial space, through the release of proinflammatory molecules, such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1, from the endothelial cells and monocytes. The release of other cytokines, such as IL-10 and IL-6, and the increased synthesis of acute phase proteins as C-reactive protein (CRP) by the liver, perpetuates the inflammatory response.

Similarly, a link exists between depression and some diseases characterized by chronic inflammation with increased levels of inflammatory cytokines. For instance, depression is common in people with rheumatoid arthritis [6]. Also, about 30–50% of patients with hepatitis C virus will develop depression after treatment with interferon [7]. Intriguingly, experimental studies showed that inducing inflammation in healthy volunteers, e.g., with a typhoid vaccine, which increases circulating IL-6 levels, leads to depressive symptoms and reduced cognitive performance [8].

Furthermore, systematic reviews and meta-analyses found that the levels of circulating pro-inflammatory cytokines, such as IL-6, IL-1β, TNF-α, and CRP, rise in acutely depressed patients, to then largely normalize after recovery [9]. As some studies showed that patients resistant to SSRI and other antidepressants continue to show elevated levels of IL-6, CRP, and other inflammatory markers, it has been hypothesized that elevated serum concentrations of cytokines might predict poor response to antidepressants [10].

Platelet Reactivity

Blood platelets are primarily known for their role in hemostasis and thrombosis, but they also have a role in inflammation and immune system. Platelets contain three different types of storage granules: dense granules, alpha granules, and lysosomes. Alpha granules store pro-inflammatory and immune-modulatory markers, such as CD62P (P-selectin), platelet factor 4 (PF-4), β-thromboglobulin (β-TG), adhesion molecules (intercellular adhesion molecule-1, ICAM-1; platelet/endothelial adhesion molecule-1, PECAM-1; the matrix-metalloproteinases type 2 and 9, MMP-2 and MMP-9), and the immune-modulatory molecule CD40L. Alpha granules are found mainly in the cytosol of platelets, are released when platelets are activated, and are responsible for the formation of platelet-monocyte aggregates. The secretion of these molecules allows for the interaction with other platelets, immune cells, and endothelial cells. Platelet degranulation is usually followed by a conformational change and aggregation. Platelets contribute largely to the development of potentially fatal ischemic events in the late stages of CVD. After adhesion to the damaged loci of the blood vessels walls, platelets promote the growth of the chronic atherosclerotic plaques and trigger the onset of arterial thrombosis consequent to the rupture of the atherosclerotic plaque. Furthermore, they maintain a local pro-atherothrombotic condition, through specific alterations of the arterial wall. On the other hand, the relationship between depression and platelet reactivity is still controversial. Some studies reported higher levels of PF-4, β-TG, and P-selectin, increased activation of platelet glycoprotein IIb/IIIa receptors, and increased platelet reactivity in patients with depression [11], while others were not able to find any difference in platelet reactivity between depressed and nondepressed patients [12].

Platelets share many biochemical similarities with the neuronal monoamine systems, mainly about the uptake, storage, and metabolism of serotonin (5-HT). The platelet and brain 5-HT transporters (SERTs) are substantially identical except for a slightly different extent of glycosylation. The role of 5-HT in depression is well established. Lower concentrations of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA), its major metabolite, have been reported in the cerebrospinal fluid and the postmortem brain tissue of depressed and/or suicidal patients [13, 14]. Postmortem brains of depressed/suicidal patients showed: (i) reduced number of serotonin binding sites in the SERT [13, 14] and (ii) increased density of 5-HT2A receptors [15]. Similar findings were reported in the platelets of suicide victims, which presented: (i) decreased maximal velocity of the SERT [16] and (ii) upregulation of 5-HT2A [17]. These alterations persist even after therapy with antidepressants and clinical improvement [18]. The gold standard treatment of depression includes the administration of drugs that affect 5-HT neurotransmission, among which selective serotonin reuptake inhibitors (SSRIs). SSRIs, in particular sertraline and citalopram, were found to normalize platelet activity indices (especially β-TG and E-selectin) [19, 20]. On the other side, a recent study demonstrated that some drugs used for angina pectoris like trimetazidine could regulate central and peripheral 5-HT in rats with myocardial infarction combined with depression [21].

Endothelial Dysfunction

Endothelial dysfunction is characterized by an alteration of nitric oxide (NO)-dependent vasodilation. Endothelial damage is a hallmark of acute cardiovascular events, where an increase of

circulating endothelial cells and a reduction of endothelial progenitor cells have been described. More surprisingly, an association between endothelial dysfunction and depressed mood was demonstrated via measures of flow-mediated dilation [22] and of plasma levels of endothelium related markers [23]. There is recent evidence of reduced levels of circulating endothelial progenitor cells in patients with coexisting depression and acute coronary syndromes [24].

Autonomic Dysregulation

The autonomic nervous system (ANS) encompasses two branches: the sympathetic nervous system, which drives physiological responses to acute stress (*fight-or-flight*); and the parasympathetic system with complementary *rest-and-digest* actions at rest. The balance between the two divisions of the ANS is fundamental. Heart rate variability (HRV), a noninvasive marker of the ANS function, refers to the beat-to-beat variations in heart rate, measured by electrocardiogram. HRV results from the balance between the two branches of the ANS at the sinus node, the parasympathetic (vagus) and the sympathetic nerves, with slowing and accelerating effects, respectively. High parasympathetic tone, by increasing the HRV, has a protective effect against possible adverse cardiac events, while high sympathetic tone, typical of situations of stress, either emotional or physical, reduces the HRV, thereby increasing the risk of malignant arrhythmias and sudden cardiac death. From a psychological perspective, while high HRV is associated with cheerfulness and calm, motivation for social commitment, resilience and well-being, low HRV is related to cognitive and affective dysregulation and psychological inflexibility, strong psychological risk factors for psychopathology. Consistently, a reduction in HRV has been found in many psychiatric disorders, such as schizophrenia, bipolar disorder (BD), conduct disorder, and autism spectrum disorders. An inverse association exists between depression severity and HRV, meaning that the more severe the depression, the lower the HRV. It is suggested that in MDD there is a relative state of sympathetic hyper-tone [25]. To support this, hallmark symptoms of depression, such as reduced social engagement, poorly flexible behavioral response to environmental changes, and somatomotor deficits, are all linked to low vagal activity since the vagus and the other cranial nerves control the peripheral structures involved in the behavioral expression of emotions [26]. In addition, patients with MDD in comorbidity with generalized anxiety disorder show the most consistent reductions in vagal activity at rest [27]. Probably, chronic worry and hypervigilance to threat may underpin chronic withdrawal of vagal activity resulting in increased morbidity and mortality. The HRV could represent an important link between MDD and CVD. The reduction of vague-mediated cardiovascular control in depression could have a disinhibiting effect on sympathetic excitatory inputs, with consequent impairment in flexibility and reactivity to environmental demands. Reciprocally, the reduction in vagal tone (and HRV) deriving from myocardial infarction could be responsible for a progressive worsening of depressive symptoms.

Although HRV changes have been found in drug-naïve depressed patients, many antidepressants, can exert diverse effects on the HRV, depending on their mechanism of action. Antidepressants with a prominent stimulation of noradrenergic neurotransmission, such as tricyclic antidepressants (TCA) and selective noradrenaline and serotonin reuptake inhibitors (SNRIs), decrease the already lower HRV seen in depression, contributing an unfavorable cardiovascular profile. In the case of TCAs, the adrenergic effect is further exacerbated by the anticholinergic properties deriving from the blockade of muscarinic cholinergic receptors. Furthermore, changes in serotonergic and dopaminergic transmission may also affect HRV. Globally, SSRIs seem to have no significant impact on HRV, regardless the response to therapy. Regarding alternative treatments, agomelatine, that blocks the 5-HT2C receptor and stimulates the melatonergic MT1 and MT2 receptors, has a significant effect on vagal tone, resulting in increased HRV; ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist, increases the sympathetic effects on the

heart thereby decreasing HRV; therefore, dose studies are needed to better assess its impact on the ANS. Transcranial magnetic stimulation (rTMS) has been shown to improve HRV in patients with MDD. Controversial data have emerged from studies that have examined the impact of electroconvulsive therapy (ECT) on HRV, requiring additional research. The vagus nerve stimulation (VNS), consisting of a surgical implant of a bipolar electrode connected to a subcutaneous generator to repeatedly stimulate the vagus nerve, improves autonomic control and reverses HRV reduction.

Strategies to increase HRV (exercise, smoking cessation, dietary changes, weight loss, intake of omega-3 fatty acids and vitamin D, stress and worry reduction, meditation) should be warmly recommended to patients with depression, especially if treated with antidepressants, to lessen their cardiovascular risk.

Sleep and Circadian Rhythm Disruption

The association between depression and sleep disorder is evident, as sleep disturbances are part of the diagnostic criteria for mood disorders. Then, it is not surprising that complaints of poor sleep occur in an estimated 50% to 90% of individuals diagnosed with depression. However, sleep alterations, such as short (< 6 h/day) or long (>8 h/day) sleep duration, and various sleep disturbances, appear to be significant determinants of CVD as well [28]. This association seems to be mediated by the impact of sleep problems on major CVD risk factors, including obesity, hypertension, diabetes, and inflammation [29]. It is known that both short and long sleep duration negatively impact upon fasting glucose levels, and short sleep is linked to increased waist circumference and triglyceride levels, independently of depressive symptoms [30]. However, a synergistic model of sleep and psychopathology in cardiovascular and metabolic disease risk has been proposed. For instance, Vgontzas et al. recently reported that short sleep duration is related to higher body mass index (BMI) in individuals reporting high emotional distress, but not in those reporting low emotional distress [31]. Similarly, subjects with both long sleep and elevated depressive symptoms developed hypertension [32].

What are the pathophysiological mechanisms called into question? Both sleep and depression are associated with unhealthy behaviors important to cardiometabolic disease risk, including smoking and physical inactivity. For instance, epidemiologic and experimental evidence shows that sleep disturbances (poor quality, polysomnography (PSG) indices of continuity, and decreased duration) are related to smoke and physical inactivity. Then, disrupted sleep influences (i) inflammation, (ii) hypothalamic-pituitary-adrenal axis, and (iii) autonomic output. First, short sleep duration and poor sleep continuity have been related to increased levels of inflammatory markers, such as IL-6 and CRP. In one study of patients with MDD, it was found that IL-6 elevation could be predicted by sleep latency and rapid eye movement (REM) density measured with all-night PSG, to suggest that disturbances of sleep initiation found in depressed patients might be partially responsible for the elevation of inflammatory markers [33]. Second, a strong link has been observed between insomnia with objective short sleep duration and both activation of the hypothalamic-pituitary-adrenal (HPA) axis and increased neurocognitive-physiologic arousal. Insomnia, jointly with HPA over-activation and consistent PSG alterations (low amounts of slow wave sleep, a short REM latency, and a high REM density), characterizes the melancholic subtype of depression, while HPA under-activation and inconsistent or inexistent sleep disturbances were found in atypical depression. Furthermore, while the alteration of HPA activity emerged as a state feature, as it tended to normalize during remission or recovery, sleep disturbances were trait features, independent of the depressive status.

Some evidence suggests that the covariation among sleep parameters, depressive symptoms, and CVD may be due to genetic influences. For example, twin studies show that common genetic variants account for significant portions of the

phenotypic correlations between depression and sleep problems in children and between depressive symptoms and coronary artery disease. These variants might be related to the bio-behavioral pathways summarized in this chapter (e.g., inflammation, HPA, autonomic imbalance); an interesting class of possibly relevant genes are the core clock genes, which are thought to regulate the endogenous circadian rhythmicity, either in the realm of glucose metabolism, adipocyte function, and vascular function or in mood regulation. A reciprocal interaction between the circadian clock system and metabolic pathways has been shown. It was demonstrated that a dysregulation of the circadian rhythm in humans is closely associated with the development of metabolic diseases, including nonalcoholic fatty liver disease (NAFLD), obesity, and type 2 diabetes. Animals deficient for clock genes or for aryl hydrocarbon receptor nuclear translocator-like protein-1 (BMAL1) go on to develop hyperlipidemia, hepatic steatosis, and defective gluconeogenesis [34, 35]. A survey of nuclear receptor mRNA profiles in metabolic tissues suggested that approximately half of the known nuclear receptors and transcriptional regulators exhibit rhythmic expression [36]. Improved knowledge of the associations between sleep and depression in relation to these mechanisms will contribute to etiological models of CVD and may provide new preventative strategies.

The Renin-Angiotensin-Aldosterone System and Neurohypophysis

The renin-angiotensin-aldosterone system (RAAS) is an endocrine system best known for its role in hydromineral balance and blood pressure regulation. As such, the RAAS system plays a fundamental role in the progression of heart failure (HF). The pathophysiology of HF is indeed characterized by the activation of different neurohormonal systems. In the early stages of HF, the sympathetic branch of the ANS and the RAAS play a compensatory role, aimed at supporting cardiac output and increasing peripheral vasoconstriction to maintain circulatory homoeostasis. However, the prolonged activation of the two systems becomes detrimental and contributes to the progression and worsening of HF, eventually leading to congestion. HF may be conceptualized as a state of neurohormonal imbalance, which cannot be counteracted even by the massive activation of the natriuretic peptide (NP) system (mostly the atrial natriuretic peptide, ANP and the B-type natriuretic peptide, BNP). The effector peptide of the renin-angiotensin system (RAS) is angiotensin-II (Ang-II). There are evidences supporting a role for the angiotensin receptor in stress-related diseases. Both physiological and psychological stressors elicit the activation of the RAS through the angiotensin type-1a receptor (AT1aR), which potentiates the intensity of stress responding. Acute stress triggers an array of neuroendocrine, autonomic, and behavioral responses, which serve as an evolutionary mechanism towards survival. However, the chronic activation of these systems has psychological, cardiovascular, and metabolic detrimental consequences. Recently, the group led by Dr. Krause has sought to elucidate the mechanisms underlying the AT1aR involvement in stress responses using the Cre-recombinarse/IoxP system and optogenetic technology in mice. They found a high expression of AT1aR in neurons within the neurosecretory subdivision of the paraventricular nucleus of the hypothalamus (PVN), projecting mostly to the exterior portion of the median eminence. Most of these neurons, which are robustly activated by a restraint stress, are glutamatergic and co-synthesize the corticotropin releasing hormone (CRH) or the thyrotropic releasing hormone (TRH). Their optical stimulation increases systolic blood pressure and circulating levels of adrenal corticotropic hormone (ACTH), corticosterone, thyroid-stimulating hormone (TSH), and thyroxine (T4). Also, their optogenetic inhibition has an anxiolytic effect, which parallels the suppression of the hypothalamic-pituitary-adrenal/thyroid axis [37]. These results point to a population of AT1aR-expressing neurons in the PVN as orchestrators of the stress response, and potential targets of treatments to alleviate stress-related diseases.

Furthermore, Ang-II increases the secretion of the antidiuretic hormone or vasopressin (ADH) from the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus. The ADH is mainly an osmotic regulator, causing water retention, and stimulating thirst to cause water repletion. However, ADH – and the related hormone oxytocin (OT) – also act on multiple brain regions as neuromodulators and influence a range of neurophysiological processes and behaviors, including feeding, anxiety, aggression, social recognition, and the stress/fear response to social stimuli. These neuropeptides are associated with complex social and emotional processing in healthy people which, if impaired, may account for some of the symptoms present in psychiatric disorders. Several studies assessed whether these neuropeptides could serve as biomarkers of psychiatric disorders. These have been recently summarized in a meta-analysis, which found no convincing evidence for significant alterations in the two neuropeptides in psychiatric disorders, mainly because of high heterogeneity across individual studies, low quality, and significant methodological limitations [38]. However, preclinical and clinical data reported the association between ADH and affective disorders (BD and MDD), probably mediated by the overactivation of the HPA axis. Postmortem brains of patients with MDD contain a greater number of ADH-immunoreactive neurons in the hypothalamic PVN. Therefore, antagonists of the ADH receptor V1b have been developed and tested in rodents as potential new strategies for the treatment of affective disorders, whose efficacy in humans does still need clarification.

Hypothalamic-Pituitary-Adrenal Axis Dysregulation

The onset, symptom severity, and the course of MDD is closely associated with psychosocial stressors. Since the HPA axis is crucially involved in the stress response, its hyperactivity has been investigated as a maintaining factor of MDD. As known, the CRH released from the hypothalamus stimulates the secretion of the ACTH from the anterior pituitary gland, and eventually the release of cortisol into the blood from the adrenal cortex. Cortisol levels show a peak in the first 30–40 min after awakening and then gradually decrease during the day, in line with a normal circadian rhythm associated with the sleep-wake cycle. Psychological or physical stressors result in HPA hyperactivity, thereby increasing plasma cortisol levels. Interestingly, individuals with depression show hypercortisolism either basal or in response to stress or after awakening, similarly to other psychiatric diseases, such as schizophrenia and BD. It has been indeed proposed that cortisol receptor antagonists and cortisol synthesis inhibitors, such as methirone, aminoglutethimide, or ketoconazole, can also be used effectively in the treatment of major depression. HPA-axis hyperactivity was also observed among the offspring of depressed patients, suggesting that it could partly reflect a marker of genetic vulnerability or an endophenotype of depression. Alterations of mineralocorticoid and glucocorticoid receptors, which act as transcriptional factors, can lead to chronic activation of the stress response resulting in atrophy of the hippocampal neurons, reduced neurogenesis and synaptic plasticity, and altered monoaminergic signaling: these alterations may lead to a depressive state. Other authors have studied the altered sensitivity of the hypothalamus to feedback signals (such as the dexamethasone suppression) in depressed patients: they found, at least in the most severe cases (depression with psychotic symptoms), a reduced or absent response to cortisol suppression.

The dysregulation of the HPA axis could be responsible for the cardiovascular somatic symptoms of depression (e.g., hypertension, tachycardia) and has also been associated with other medical conditions such as hypertension, high lipids, insulin resistance, and obesity. It is known that patients with HF have high circulating corticosteroids due to neuroendocrine activation. Higher serum and salivary levels of both cortisol and aldosterone are independent, complementary, and incremental predictors of all-cause mortality risk in patients with systolic and nonsystolic

chronic or acute HF of any cause and severity. Aldosterone participates in numerous detrimental processes that lead to HF progression such as inflammation, fibrosis, endothelial dysfunction, hypertrophy, hypertension, and arrhythmia. Cortisol acts primarily through the glucocorticoid receptor: mineralocorticoid receptor has equal affinity for both cortisol and aldosterone, but since cortisol concentrations are 100 to 1000 times higher than aldosterone, it is hypothesized that the mineralocorticoid receptor is predominantly occupied from cortisol in those tissues that are not classically a target of aldosterone such as cardiac muscle. Generally, cortisol acts as a mineralocorticoid receptor antagonist, but in HF, there is a high cellular oxidative stress and cortisol can act as a mineralocorticoid receptor agonist. Chronic hypercortisolism, as in Cushing's syndrome, can have deleterious cardiovascular effects and affected patients often develop central obesity, hypertension, and diabetes mellitus, in turn cardiovascular risk factors. Antagonists of mineralocorticoid receptors (such as spironolactone or eplerenone), used in the treatment of patients with HF, effectively reduce adverse cardiac remodeling and hospitalization, with improved survival.

Neurotrophins

Neurotrophins (NTs) are a large family of dimeric polypeptides that include four similar proteins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5). The activity of these factors has been implicated in axonal growth, synaptic plasticity, survival, differentiation, and myelination. BDNF in the brain is active in the hippocampus, cortex, and basal forebrain areas, vital to learning, memory, and higher thinking.

It has been shown that serum/plasma levels of BDNF are lower in patients with MDD than in healthy controls and increase in response to antidepressant treatment or ECT. Therefore, BDNF can be considered as state rather than a trait marker of MDD. A possible pathogenetic theory correlates chronic stress with BDNF; chronic stress is an environmental trigger of several psychiatric disorders, including depression. It is demonstrated that chronic stress has neurotoxic effects, including damage to hippocampal cells that may underlie symptoms of depression. Also, several studies reported a correlation between polymorphisms of BDNF and depression. The rs6265 G/A variant, in which a valine changes to a methionine in position 66 of the BDNF protein (Val66Met), is related to a higher risk of depression: individuals with the Val/Val (G/G) genotype have a stronger depressive trait [39]. However, more recently, the Val66Met variant was found to correlate not to MDD risk per se, but with late-life depression. Plausibly, Val66Met in the BDNF gene predicts the response to antidepressants in MDD, in fact serum plasma levels of BDNF in patients with MDD increase after antidepressant treatment or ECT.

In addition to its important role in the CNS, there is increasing evidence that BDNF is also involved in cardiovascular development and pathophysiology. BDNF is known to play a protective role in the heart by inducing angiogenesis and vascular remodeling, by the upregulation of pro-survival factors, and by promoting the neovascularization of ischemic tissue by recruiting endothelial cells and regulating the survival of cardiomyocytes. BDNF and its receptors are expressed in various tissues, including the heart, endothelial cells, macrophages, vascular smooth muscle cells, and atherosclerotic coronary arteries. Recent studies showed BDNF to have a regulatory impact on cardiac progenitor cells, contribute to cardiac repair and attenuate cardiac dysfunction [40]. Moreover, in a recent investigation, plasma BDNF concentration was found to be negatively associated with the levels of triglyceride, LDL-cholesterol and fibrinogen, presence of diabetes mellitus, male sex and age, and positively with high-density lipoprotein cholesterol (HDL) level and platelet count in people with angina pectoris [41]. Consequently, it seems that a higher serum level of BDNF can be associated with a lower risk of CVD. Carriers of the Val66Met variant have higher BMI and CRP levels than Met carriers.

Lifestyle and Metabolic Syndrome

The association between depression and CVD is thought to be mediated the so-called metabolic syndrome, encompassing obesity, diabetes, hypertension, and dyslipidemia. The exact mechanisms linking depression and metabolic syndrome remain largely unclear. Some suggest that metabolic syndrome could represent the outcome of many unhealthy lifestyle habits of depressed patients, such as poor diet, physical inactivity, tobacco and alcohol use. Indeed, adjusting for lifestyle-related factors reduced the association between depression and adverse lipoprotein patterns (lower HDL level and higher triglyceride level). Depressed patients are more prone to inadequate diets that are often characterized by an excessive intake of highly palatable food with high content of sugar, starches, and fat, and a low consumption of fish, vegetables, and cereals. A protective potential against depression is yielded by the adherence to the Mediterranean dietary pattern, which improves endothelial function, decreases pro-inflammatory cytokines, reduces plasma homocysteine levels, and induces favorable changes in insulin/glucose homeostasis. The high content in fruits, nuts, vegetables, beans, cereals, olive oil, and fish, and the low content in meat and dairy products, ensures the adequate intake of nutrients with a key role in the CNS. Vitamins B6 and B12, together with folic acids, are fundamental in the homocysteine cycle. Their deficit may impair the synthesis of catecholamines, serotonin, and other monoamine neurotransmitters. Moreover, it determines an accumulation of homocysteine and its metabolites, with excitotoxic effect on NMDA glutamate receptors. Additionally, fish consumption, rich in v3-polyunsaturated fatty acids (v3-PUFA), seems to inhibit the synthesis of pro-inflammatory cytokines, particularly TNF-α and IL-β. Olive oil is a good source of monounsaturated fatty acids (MUFAs, oleic acid), which have antioxidant properties, increase the d-9 desaturase enzyme activity, crucial for the properties of neuronal membranes, and improve the binding of serotonin to its receptor. A recent line of research suggests that dietary barley (1.3) beta-D-glucan (β-D-glucan), a water-soluble polysaccharide, increases the levels of histone H4 acetylation, thereby ameliorating glucose tolerance, mood, anxiety, and cognition in obese mice exposed to chronic psychosocial stress. This is accompanied by the upregulation of the hippocampal BDNF and its receptor, the tropomyosin-related kinase B TrkB [42].

Also, a sedentary lifestyle and a negative self-perception due to the stigmatization of obesity could lead to an increased risk of depression. Growing evidence suggests that exercise reduces depressive symptoms in CVD patients, especially aerobic exercise, which seems to be effective by the end of a 16-week intervention. Exercise may be effective in part because it involves behavioral activation, a key component of cognitive-behavioral therapy (CBT) for depression. Exercise has well-documented cardiovascular benefits. Exercise training is associated with several beneficial physiologic changes, such as improvements in ANS and HPA-axis functioning, endothelial function, hypertension, dyslipidemia, insulin resistance, and inflammation. Exercise affects depression, CVD risk factors, and CVD outcomes so that it seems a promising intervention for depression, together with good dietary habits. Furthermore, exercise has been proven to revert the downregulation of the BDNF/TrkB signaling in the prefrontal cortex of obese male mice [43].

Increased smoking and alcohol consumption are well documented in depression. Park and Lee reported that current smokers are 3.99 times more likely to suffer from depression than those who had never smoked. In addition, depressed people smoke more cigarettes and are less likely to quit smoking. Nicotine might cause depression through direct or indirect influences on neurotransmission (noradrenergic neurotransmission and/or hippocampal BDNF). Alcohol consumption is associated with an increase in the prevalence of depression as well, particularly in women in relation to reduced alcohol tolerance, as compared to men. It is biologically plausible that alcohol can act as a depressant of the CNS;

reciprocally, depression itself can induce alcohol consumption.

However, some authors reported that the association between (i) low HDL cholesterol and melancholic depression, and (ii) high total and LDL cholesterol and atypical depression, remained even after adjusting for covariates. A hypothesis is that depression and metabolic syndrome would share common pathophysiologic mechanisms, such as the above described alterations of the stress system, including the HPA-axis, the ANS, the immune system, and platelet and endothelial function.

From an epidemiological perspective, obese subjects (defined as high BMI or high abdominal circumference) are 55% more likely to develop depression over time. Like depression, obesity can be viewed as a low grade inflammatory state. The white adipose tissue, especially in the abdominal area, is an active endocrine organ that produces cytokines with paracrine functions, such as TNF-α, resistin, IL-6, and CRP. IL-6 and TNF-α have important effects in glucose and lipid metabolism and regulation, such as: (i) inhibition of the action of lipoprotein lipase and stimulation of lipolysis, leading to dyslipidemia; (ii) phosphorylation of both the insulin receptor and its substrate, IRS-1, leading to impairment of the insulin signaling pathway. Elevated levels of IL-6 and TNF-α may be responsible for alterations in vasodilation of resistance vessels and ultimately hypertension, by inducing endothelial expression of chemokines and adhesion molecules. Furthermore, adipocytes secrete leptin, a hormone which acts at the hypothalamic level as an anorexigenic signal. Leptin has been shown to influence hippocampal and cortical structure through its actions on neurogenesis, axon growth, synaptogenesis, and regulation of dendritic morphology. Leptin-deficient mice (ob/ob), jointly with an obese phenotype, exhibit neurodegenerative changes – lower brain weight and cortical volume, and reduced expression of total neuronal and glial proteins – which can be rescued by leptin replacement [44]. Animal models of chronic stress posit an antidepressant-like role for leptin [44]. Also, more depressive behaviors were observed in diet-induced obese mice fed a high-fat diet, with respect to a control diet. However, in this model leptin seemed to lose its antidepressant-like effect: only diet substitution from high-fat diet to control diet improved the depressive state [45]. This in in line with the hypothesis that depressed people, similarly to obese people, although having high circulating levels of leptin in proportion to their greater fat mass, might develop a resistance to the effects of leptin. Intriguingly, leptin could modulate the synaptic availability of 5-HT and dopamine, neurotransmitters classically involved in depression, given the high proportion of 5-HT and dopamine neurons, respectively, in the raphe nuclei and in the VTA, which express leptin receptors. Another peripheral hormone participating in either homeostatic or stress-induced feeding behavior is ghrelin, a gut-derived orexigenic hormone, acting at the level of its receptors (GHSR) in the hypothalamic circuits. Evidence has emerged about the role of ghrelin in depression: (i) elevated levels of ghrelin were observed in animal models of depression; (ii) peripheral administration of ghrelin to wild-type animals reverted depressive behavior; (iii) Ghrs-null mice exhibited more depressive-like symptoms than wild-type littermates. Interestingly, wild-type mice, but not Ghrs−/− mice, showed hyperphagia in response to social stress [46]. The activation of ghrelin signaling pathways in response to chronic stress could represent a homeostatic adaptation that helps an individual coping with stress, but at the expense of increased caloric intake. Of note, ghrelin cells are stimulated by stress-induced catecholamines. As described for leptin, ghrelin has emerged as a potent modulator of the mesolimbic dopaminergic circuits.

Moreover, depression is in turn predictive of the development of obesity through long-term activation of the HPA axis, as cortisol inhibits the enzymes mobilizing lipids in the presence of insulin, a process mediated by glucocorticoid receptors found in fat stores, especially in intra-abdominal visceral fat.

Identification and Treatment of Depression in Patients with CVD

The American Heart Association recommends that CVD patients are routinely screened for depression. The answers to two simple questions – "*During the past month, have you often been bothered by feeling down, depressed, or hopeless?*" and "*During the past month, have you often been bothered by little interest or pleasure in doing things?*" – yield a 90% sensitivity and 69% specificity and a negative likelihood ratio of 0.14, essentially ruling out depression. Alternately, instruments with good diagnostic characteristics, such as the depression module of the Patient Health Questionnaire (PHQ-9), can be introduced in the routine vital sign gathering of CVD patients. Notwithstanding this, in general practice depression is recognized and diagnosed in less than 25% of patients with CVD, the remaining being at risk of more severe clinical outcomes.

Diagnosis should be then followed by initiation of an adequate antidepressant treatment. Effective treatments for depression in CVD include pharmacological (antidepressant medications), nonpharmacological somatic (e.g., ECT), and evidence-based psychotherapeutic strategies (e.g., CBT, interpersonal therapy [IPT]). Current guidelines for antidepressant treatment suggest 6–12 weeks of acute treatment followed by a continuation phase of 3–9 months to maintain therapeutic benefit. However, antidepressant drugs are associated with a potential for cardiac toxicity, often related to the presence of preexisting cardiac disease or other factors that might independently increase the risk of arrhythmia. The cardiovascular safety profile will be specifically discussed for the different classes of antidepressants.

SSRIs, such as citalopram, sertraline, and paroxetine, are recommended as first-line drug therapy, due to their effectiveness, safety profile, cost-effectiveness, and best supporting data in CVD populations. Among them, sertraline has been the most commonly studied and is often considered to be the first-line drug of choice in patients with ischemic heart disease. At therapeutic doses, the most common side effects of SSRIs are sexual dysfunction and weight gain. Also, adverse effects might be generated from the inhibition of the 2D6 isoenzyme of the cytochrome P-450 by fluoxetine and paroxetine. SSRIs are unlikely to be associated with cardiovascular adverse events. Nonetheless, there are reports of orthostatic hypotension, mild bradycardia, and conduction abnormalities under SSRIs therapy. Some SSRIs, such as citalopram and escitalopram, are known to cause a dose-dependent QTc prolongation. Therefore, their use should be accompanied by QTc monitoring and avoided in presence of QTc prolongation. In a large population of CVD patients, major adverse cardiac events have been reported to be 1.5-fold more common in patients taking SSRIs. Since SSRIs are known to alter platelet activation and aggregation leading to impairment in hemostasis, their use could potentially increase the risk of perioperative bleeding, transfusion, morbidity, and mortality in cardiac surgical patients. However, a recent study found no significant differences in perioperative outcomes between patients under SSRIs and matched controls and concluded that SSRIs interruption to reduce the risk of perioperative bleeding and transfusion is unwarranted to and may risk destabilization of patients' psychiatric condition.

Second-line therapy for depression includes SNRIs, trazodone, mirtazapine, and bupropion. SNRIs seem able to increase sympathetic tone, with consequent modest increase of heart rate, increase of arterial pressure, and increase of sympathetic influence on the HRV. Venlafaxine could block the cardiac conductance of the sodium channel and at toxic doses could increase the systemic blood pressure and cause a QTc prolongation. Duloxetine has been less studied, and no clear indications are given in relation to CVD. Although a study of a large population of CVD patients found fewer adverse cardiac events than expected in patients taking SNRIs, caution is required in geriatric populations. Bupropion and mirtazapine are often used in clinical practice, but remain largely unstudied. Aside the risk of hypertension, bupropion was found to be safe in patients with cardiac conduction disease and left ventricular systolic dysfunction. Mirtazapine has

been noted to cause weight gain and increased body fat mass, but no association with CVD was found.

TCAs and monoamine oxidase inhibitors are contraindicated in CVD patients. In a large population of CVD patients, major adverse cardiac events occurred with 2.5 times higher frequency in patients under TCAs. TCAs can cause significant inhibition of central cholinergic neurotransmission and reduced neuronal reabsorption of norepinephrine, which cause alterations in the sympathovagal balance. TCAs also block alpha-adrenergic receptors, reducing systemic vascular resistance and causing (orthostatic) hypotension. TCAs also inhibit the conductance of the sodium channel, resulting in slower conduction within the His fibers-Purkinje and of the ventricular myocardium and in prolongation of the QRS.

Although pharmacologic-based approaches to treat depression have a significant beneficial impact on platelet/endothelial activation markers, inflammation, and sympathovagal balance, trials of antidepressant pharmacotherapy in patients with CVD failed to demonstrate a clear impact on cardiovascular events and outcomes. On the other hand, randomized and observational trials showed that pharmacotherapy for depression might decrease the risk of future cardiovascular events.

Nonpharmacological somatic therapies are often useful in clinical practice to treat severe form of depression or drug-resistant depression; among them ECT is one of the most effective. The ECT is associated with significant changes in cardiovascular physiology and has a significant implication in patients suffering from a CVD. The ECT causes a generalized seizure activity, which induces an initial parasympathetic activity, that coincides with the tonic phase of the seizure, followed by a generalized sympathetic activity, associated with catecholamine release during the clonic phase. The double activation of the two branches of the ANS has a significant hemodynamic impact. Due to the sympathetic discharge, tachycardia and hypertension may develop. The sudden increase of the rate/pressure product may place the myocardium at risk for ischemia by a sudden increase in myocardial oxygen consumption. Despite this, ECT is administered safely even in patients with cardiac risk factors, although it is generally recommended to wait for a period of 90 days following an acute coronary event to initiate ECT.

To maximize improvements in health outcomes and quality of life, CVD patients with depression may benefit most from interventions that simultaneously target both depression and cardiovascular risk factors. Studies about non-pharmacological treatment of depression and CVD are relatively small and the findings are equivocal. In a recent review and meta-analysis, CBT resulted more effective than usual care at improving depression and quality of life in patients with HF. It was demonstrated that CBT-based interventions reduced ischemia and prevented cardiac events in the following months [47]. It is also possible that other psychosocial interventions, such as IPT, may prove to be effective, but further research is needed to address these questions.

Finally, collaborative care models emerged in several studies as promising interventions to ameliorate depression, mental health status, medication adherence, cardiac risk factors (cholesterol and blood pressure), and cardiac symptoms.

Conclusions

In 1628, William Harvey, the pioneer of blood circulation, warned that mental suffering and anxiety could disturb the heart and the circulatory system. For him, “The heart of animals is the foundation of their life, the sovereign of everything within them, the sun of their microcosm, that upon which all growth depends, from which all power proceeds.” The symbolism of myth, poetry and holy has put the heart at the center of the body, as the headquarter of the mental and spiritual life in humans. The link between the heart and emotions is also revealed by transcultural linguistic expressions, such as “sick at heart,” “heartbroken,” or by the depressed patients frequently complaining of pain in their chest. Here, we showed that the relationship between brain and heart, far from being just metaphorical, lies in a

psycho-neuro-hormonal-cardiovascular axis. We described the overlapping pathophysiological mechanisms involved in the association between depression and CVD, which include inflammation, platelet reactivity, autonomic dysregulation, circadian rhythm and sleep disruption, hormone imbalance, neurotrophins, lifestyle, and metabolic syndrome. We strongly recommend physicians to explore depressive symptoms in people with CVD and to assess the cardiovascular function in subjects presenting with depression. Interventions that simultaneously target both depression and cardiovascular risk factors might indeed substantially improve health outcomes and quality of life.

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