REVIEW ARTICLE

Cardiovascular Disease and Depression

Enfermedad cardiovascular y depresión

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ABSTRACT

Depression and cardiovascular disease (CVD) are two leading causes of disability, impacting quality of life and increasing healthcare costs. There is a bidirectional relationship between them: depression is a risk factor for developing CVD and worsens prognosis in CVD patients. CVD in turn increases the incidence of depression and worsens its prognosis. Biological factors involved in both pathologies include autonomic dysfunction, chronic inflammation, and increased platelet reactivity. It is recommended to screen for depression during cardiology consultations, using tools such as the Patient Health Questionnaire (PHQ-2). Treatment should be comprehensive, combining antidepressants, psychotherapy, physical exercise, and mindfulness practices. Initially focused on exercise, cardiovascular rehabilitation (CR) has evolved to encompass lifestyle modification, which has been shown to improve depression and overall well-being in CVD patients.

Keywords: Cardiovascular disease - Depression - Health care quality.

RESUMEN

Existe una relación bidireccional entre ambas: la depresión es un factor de riesgo para desarrollar ECV y empeora el pronóstico en pacientes con ECV. La ECV a su vez aumenta la incidencia de depresión y empeora su pronóstico. Los factores biológicos implicados en ambas patologías incluyen la disfunción autonómica, la inflamación crónica y una mayor reactividad plaquetaria. Se recomienda la detección de la depresión en la consulta cardiológica, usando herramientas como el cuestionario de salud del paciente (PHQ-2). El tratamiento debe ser integral, y combinar antidepresivos, psicoterapia, ejercicio físico y prácticas de mindfulness. Inicialmente centrada en el ejercicio, la rehabilitación cardiovascular (RCV) ha evolucionado para abarcar la modificación del estilo de vida, lo cual ha demostrado mejorar la depresión y el bienestar general en pacientes con ECV..

Palabras claves: Enfermedades cardiovasculares - Depresión - Calidad de la atención médica.

INTRODUCTION

Depression is characterized by persistent sadness and loss of interest in activities normally enjoyed, as well as the inability to carry out daily activities, for at least two weeks (WHO, 2021). (1) According to the World Health Organization, cardiovascular disease (CVD) and depressive disorders are the most common causes of disability, affecting 1 in 5 adults during their lifetime. (2) Major economic and health system indicators reveal rising medical costs, increased utilization of health services, and loss of productivity in patients with these pathologies. (3-6) Furthermore, CVD and depression profoundly impact overall quality of life; (7,8) depression being probably the most important determinant of overall quality of life. There is a bidirectional relationship between CVD and the development of depressive disorders. (9) Depression is a major cause of morbidity and poor quality of life among patients with CVD and is also considered an independent risk factor for major adverse cardiovascular events. (10) Therefore, it is imperative to know that depression is considered a risk factor for the development of CVD in healthy individuals, and implies worse outcomes in those with a diagnosis of CVD .

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Since 2008, the American Heart Association (AHA) has recommended systematic screening for depression in patients with established CVD, and in 2014, the same cardiological society added that depression should be considered a risk factor for poor outcome in patients with acute coronary syndromes. (1) Currently, the presence of depression after myocardial infarction is independently associated with a 2- to 4-fold increased risk of cardiovascular events at follow-up. (11,12) This risk is directly proportional to the severity of depression. (13) The risk is higher in patients refractory to antidepressant treatment. (14) Similarly, depression is associated with a higher rate of cardiovascular events after coronary artery bypass grafting (CABG). (15)

A recent study among patients who suffered out-of-hospital cardiac arrest showed that those diagnosed with depression or anxiety had higher long-term mortality rates, suggesting that psychological and neurological rehabilitation intervention for survivors may improve long-term survival. (16)

Like chronic noncommunicable diseases, depression is considered a systemic and multidimensional pathology, affecting both body and mind, relationships, work performance and social insertion, with a strong tendency to chronicity and recurrence. (17,18)

METHODS

A review was carried out by selecting the most significant papers related to this topic. The PubMed, Lilacs and Scielo search engines were used, employing the following word combinations in the title and abstract: "depression AND cardiovascular health"; "depression AND cardiology"; "depression AND cardiovascular disease", and their equivalents in Spanish. In addition, the search was supported by the use of the tool offered by Open Alex.

The Consensus on Psychosocial Aspects of Cardiovascular Disease written by the Council on Psychosocial Aspects of the Argentine Society of Cardiology (SAC) was used as reference. (19) In addition, the Position Document for Stress Management written by the working group of the Council on Psychosocial Aspects of the SAC was used. (20)

RESULTS

Pathophysiology

Multiple biological mechanisms have been identified as contributing to the less favorable prognosis observed in patients with both CVD and depression. Among these factors are the influence of unhealthy lifestyle habits, alterations in the autonomic nervous system, imbalance in the neuroendocrine axis, chronic inflammatory processes, insulin resistance, and increased platelet activity. These mechanisms are not only present simultaneously, but also interact with each other in a complex manner, jointly affecting cardiac function and neuropsychiatric condition. Consequently, the co-occurrence of depression and CVD represents a multifactorial interaction that exacerbates the risk of adverse health outcomes. (21)

Patients with depression are more susceptible to engage in behaviors that impair health, such as smoking, physical inactivity, and poor diet, which, together with low adherence to recommended therapeutic interventions, enhances CVD progression and decreases recovery probability. (22,23) Depression and prevalent forms of CVD, such as heart failure and ischemic heart disease, share a strong relationship with autonomic dysfunction, which acts as a trigger for adverse cardiovascular events. This autonomic dysfunction manifests itself through increased sympathetic activity and decreased parasympathetic activity, which, in depressed patients, translates into increased resting heart rate, reduced heart rate variability, and increased blood pressure. These autonomic alterations contribute to structural and functional pathologies such as left ventricular hypertrophy, increased risk of ventricular arrhythmias and endothelial dysfunction, in addition to mismatches in myocardial tissue oxygen supply and demand, factors that increase the risk of myocardial ischemia. (24,25)

On the other hand, depression is closely related to hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which responds to stress with the release of glucocorticoids, such as cortisol. In depressed individuals, overstimulation of the HPA axis leads to chronic hypercortisolemia, which is implicated in the development of arterial hypertension and early atherosclerosis. Excess cortisol elevates the risk of thrombotic cardiovascular events and the development of diabetes mellitus, complications that may accelerate CVD progression. (26-28)

Platelet function is also abnormal in depressed patients, who tend to exhibit increased platelet reactivity, reflected in the release of mediators such as platelet factor 4 and beta-thyroglobulin. This intensified platelet activation could act as an additional factor in the predisposition to acute cardiovascular events, by promoting a prothrombotic environment and, consequently, favoring the occurrence of events such as acute myocardial infarction. (29)

Regarding the inflammatory profile, patients with depression usually reveal elevated levels of proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), in addition to other inflammatory markers such as C-reactive protein (CRP) and adhesion molecules. This chronic inflammatory condition is considered an intermediate factor of great relevance in the pathogenesis of CVD, as it promotes endothelial dysfunction, contributes to the development of atherosclerosis, and increases the risk of major cardiovascular events. Inflammation, then, emerges as a key link between depression and CVD, standing out as one of the most influential pathological mechanisms in this association. (30) This confluence of factors suggests that the relationship between depression and CVD is not merely additive

but rather responds to a complex interaction that exponentially increases cardiovascular risk in these patients. In this context, intervention in both physical and psychological factors is crucial to improve the prognosis of these patients and reduce the risk of adverse health outcomes.

Diagnosis

Detection of depression in the cardiology consultation

In recent decades, clinical practice guidelines on CVD prevention suggest that depression should be screened for and treatment offered to patients with clinically significant depression. (31)Similarly, the European Society of Cardiology guidelines for the diagnosis and treatment of heart failure suggest that it is good practice to routinely screen for depression using a validated questionnaire. (32) However, most cardiologists do not believe they have a role in screening for depression in their patients and understand that it is the responsibility of someone else, such as a nurse, rehabilitation program, or family physician. (33) Given that depression is the main factor of quality of life in cardiac patients, cardiologists should not shirk their responsibility to ensure that depression is detected.

Individuals who have had an acute coronary syndrome have a prevalence of depression two to three times higher than that of the general population. Depression is often repressed or suppressed in the hospital because of the initial denial of affect. Therefore, patients should be re-screened for depression one to two months after the acute event. In studies as early as 50 years ago, non-deniers seemed to shed their fears more slowly and let down their guard more quickly than deniers. As discharge approached, the trajectories of anxiety and depression scores increased. (34,35) Patients with chronic heart failure have a frequency of depression 3 to 5 times higher than that of the normal population. Therefore, all these patients should be examined at least once a year.

Most studies have focused primarily on major depression or on a self-report scale intended to "diagnose" major depression. Scales are tools to evaluate and assess the severity of the depressive condition, adding the impact of the depression on the patient's life to the subjective impression of the professional. They will also enable to monitor symptoms and evaluate response to treatment. Some are used as a first screening step requiring a subsequent "clinical diagnosis". Others have satisfactory psychometric properties to "diagnose" major depressive disorder in a single step. Self-report questionnaires include the Patient Health Questionnaire (PHQ), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Cardiac Depression Scale (CDS), and the Center for Epidemiologic Studies Depression Scale-10 (CES-D). Most of these scales are available and have been validated in many different languages. (36-40) Currently, their use as diagnostic tools is not recommended.

An AHA scientific advisory group suggested that the PHQ-2 may be the most useful questionnaire for screening patients with CVD. (41) The PHQ-2 consists of two items that ask about patients' mood and their experience of anhedonia in the last 2 weeks. (Figure 1) Patients who screen positive (score ≥ 3) should be evaluated with the 9-item patient health questionnaire (PHQ-9). The PHQ-9 expands the PHQ-2 to include seven additional DSM-IV symptoms of depression. (42,43) Those who are tested positive for depression in the PHQ-9 should be treated with a multidisciplinary, team-based approach that includes primary care providers and mental health clinicians. (44)

Treatment

Interventions in patients with cardiovascular disease

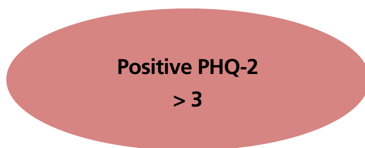
Treatment of depressive disorders in patients with CVD includes primary prevention and secondary prevention strategies. Primary prevention focuses on identifying possible risk factors for depression. These are clinical and symptomatic factors that should alert the treating professional to the existence of a possible depressive disorder. (45,46) (Table1) There are a series of recommendations for these patients that range from the application of selective physical activity programs, healthy diet, sleep hygiene, control of exposure to screens, to meditation and/or mindfulness (which promotes focusing exclusively on the present)

The approach to depression in adults with CVD should be comprehensive and include all psychotherapeutic, psychosocial and pharmacological interventions that contribute to improving well-being and functional capacity. (21) Antidepressants are used more frequently than psychological or social interventions, although mild depression usually responds positively to psychotherapy and other therapeutic alternatives. The search for immediacy and quick resolutions leads to the use of pharmacotherapy as the first measure, although studies have shown that the combination of psychotherapy, antidepressants, physical exercise and meditation or mindfulness practices provide better results in the short and long term.

Non-pharmacological treatment of depression

The effectiveness of psychological and behavioral interventions in improving cardiovascular outcomes has shown variability, reflecting the complexity of the interaction between psychological treatment and cardiac health outcomes. Science-based therapies, such as cognitive-behavioral therapy (CBT), have shown superior results compared with usual care in reducing the intensity of depressive symptoms in patients with heart failure and a diagnosis of depression, suggesting a benefit in the co-management of both conditions. (47) During a 2-year follow-up period, a meta-analysis that included clinical trials focused on psychological and behavioral interventions revealed that psychotherapy is associated with a significant reduction in mortality, up to 28% lower compared to

How often have you had discomfort due to the following problems?	Never	Several days of the week	More than half the days of the week	Most days of the week
Little interest in the last 2 weeks	0	1	2	3
Negative feelings, depression or unhappiness in the last 2 weeks	0	1	2	3



In case of a positive PHQ-2, continue with the PHQ-9 questionnaire.

Fig. 1. Two-item Patient Health Questionnaire (PHQ-2).

Clinical factors	Symptomatic factors
-History of unexplained depression	-Chronic pain
-Family history of mood disorder	- Fatigue
-Psychosocial adversity. Complex grief	-Sleep disorders
-Chronic diseases (DM, CVD, neurological)	-Anxiety
-Psychiatric pathology	-Peripartum period
-Hormonal changes in women	

Source: Parikh SV, et. al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder. The Can J Psychiat. 2016; 61(9):524-39. (45). CVD: cardiovascular disease; DM: diabetes mellitus

Table 1. Clinical and symptomatic factors leading to suspicion of possible depressive disorder.

control groups. (48) Furthermore, the benefits of psychological intervention were more evident in patients who started treatment within the first 2 months after an acute cardiac event, highlighting the importance of the time of intervention in treatment efficacy (49-51).

The ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) study was a randomized clinical trial that explored the effects of CBT in post-myocardial infarction patients with symptoms of depression or low social support. Patients were assigned to receive either conventional care or a CBT intervention, and the results showed significant improvements in psychosocial indicators, such as a reduction in levels of depression and an increase in perceived social support in the treated group. However, these psychosocial benefits did not translate into improved event-free survival, suggesting that although CBT improves certain aspects of quality of life, its impact on mortality or recurrent cardiovascular events in this specific setting may be limited. (52)

Physical exercise has emerged as an effective additional therapy against depression in patients with CVD. In a secondary analysis of the ENRICHD study, patients with depression who maintained adherence to regular physical exercise 6 months after acute myocardial infarction had 38% to 52% lower rates of major events (fatal and nonfatal) during a 4-year follow-up compared with those who did not exercise consistently. These findings highlight the potential value of exercise as an adjunctive measure to reduce mortality and the incidence of new infarctions in post-infarction patients, especially in those at increased risk of adverse events due to depressive symptoms or lack of social support. (53)

In addition, practices such as meditation and mindfulness, specifically mindfulness-based cognitive therapy, have been recommended to prevent the recurrence of depressive symptoms. Several studies have shown that the latter can help patients manage recurrent depressive symptoms and reduce emotional reactivity, which could offer additional benefits in emotional regulation of patients with CVD, although the evidence regarding its direct impact on cardiovascular health is still under study. (54-67)

Altogether, these interventions suggest that a comprehensive approach including psychological treatment, physical exercise, and mindfulness practices may contribute to the improvement of mental condition and reduce the risk of recurrent cardiac events, although further studies are required to fully understand the magnitude of their effects on mortality and CVD progression in this group of patients.

Role of cardiovascular rehabilitation

Although cardiovascular rehabilitation (CVR) was initially introduced as an exercise-focused intervention, its scope was subsequently broadened to become a more comprehensive lifestyle intervention, with

exercise as the main component and four additional elements including dietary modification, risk factor management, stress reduction, and patient education. This development is relevant because of the growing evidence available suggesting that lifestyle change, including sleep hygiene, either individually or in combination with exercise, can contribute to improving depression. (68-70) Even in countries with limited medical resources, the virtual (home-based) modality has demonstrated positive impact on both quality of life and psychological well-being. (71) In a recent experience in our country, it was observed that the positive effects of referral to Mental Health complemented the benefits of CVR. (72) Undoubtedly, the improvement in the individual's mood favors adherence and compliance with rehabilitation treatment

Pharmacological treatment of depression

When addressing psychopharmacological treatments for depression in patients with CVD, it is essential to rely on sound clinical guidelines to guide daily medical practice. These include the Canadian Network for the Management of Mood and Anxiety Disorders (CANMAT) Guidelines for the Management of Depression and the UK National Institute for Health and Care Excellence (NICE). (45,46) The NICE guidelines are particularly valuable because of their comprehensive review of scientific evidence. They recommend the use of antidepressants in cases of moderate to severe depression or when symptoms persist without improvement. Within the antidepressants, they suggest selective serotonin reuptake inhibitors (SSRIs) as the preferred option for efficacy, although no SSRI has demonstrated superiority over another in general terms. (73-77) However, the characteristics of each drug allow choosing the most appropriate one for each patient's profile. (78)

The effectiveness of SSRIs in patients with CVD has been supported in clinical trials. The SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) trial led by Glassman et. al., evaluated their use in 369 post-ACS patients with major depression. Although the Hamilton Depression Scale (HAM-D) scores showed no significant differences between the sertraline and placebo groups, sertraline-treated patients had higher response rates and clinical improvement in the overall group. In addition, participants with a history of depressive episodes or with depressive disorders of greater severity experienced a more pronounced improvement in their HAM-D scores. (74) Pizzi et. al. also observed that sertraline, compared with placebo, produced a significant improvement in depression scores in patients with coronary artery disease after 20 weeks. (75) In the UPBEAT (Understanding Prognostic Benefits of Exercise and Antidepressant Therapy for Persons with Depression and Heart Disease) study, sertraline, aerobic exercise, and placebo were compared in a sample of 101 patients with coronary artery disease and depressive symptoms. Both the sertraline and exercise groups showed significant improvements in depressive symptoms compared to placebo, with no considerable difference between the effects of sertraline and exercise, reinforcing the value of exercise as an adjunct in the treatment of depression in this population. (77)

Another recent study with an extended follow-up of 8.1 years and a sample of 300 patients showed that escitalopram reduced the incidence of major adverse cardiac events after acute coronary syndrome (ACS) compared to placebo (40.9% vs. 53.6%) after 24 weeks, confirming its benefit in this context. (79)

The EsDEPACS (Escitalopram for Depression in ACS) trial, which evaluated 300 patients with ACS and depression, showed that escitalopram was superior to placebo in reducing depressive symptoms at 24 weeks and up to 1 year of follow-up. (80) These results reinforce the safe and effective profile of SSRIs for the treatment of depression in patients with recent ACS and stable coronary artery disease, making them suitable for the management of depression in this high-risk group. In conclusion, the evidence supports the use of sertraline and escitalopram as treatments of choice in patients with depression and cardiovascular disease, providing a benefit both in the reduction of depressive symptoms and in the reduction of adverse cardiac events.

CONCLUSION

The relationship between depression and cardiovascular health is an area of growing interest in medical research, with an extensive body of evidence supporting its bidirectional link. Depression can exacerbate morbidity and mortality associated with cardiovascular disorders, in addition to affecting the quality of life and prognosis of these patients. It is imperative to adopt a multidimensional approach that includes mental health assessment and treatment strategies in the context of cardiovascular care. The search for immediacy and quick resolutions leads to the use of pharmacotherapy as the first treatment measure, although studies have mostly evidenced that the combination of psychotherapy, antidepressants, physical exercise and contemplative practices, provide better short- and long-term outcomes. Overcoming mental health disparities and barriers involves health policy interventions, education, training, innovation in medical care, and diversification of cardiology.

In conclusion, recognition of the interaction between depression and cardiovascular health is essential to improve outcomes and encourage a multidisciplinary approach to care appropriately integrating mental and cardiovascular health.

"*Every affection of the mind accompanied by pain or pleasure, hope or fear, produces an agitation whose influence extends to the heart.*"

Willam Harvey

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material).

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