CME 3

Depression as a Risk Factor for Cardiovascular Disease

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Abstract

Evidence supporting a link between clinical depression and cardiovascular disease has expanded rapidly over the last 20 years. Depression has been found to be an independent risk factor for the occurrence of cardiac disease in multiple studies. There is increasing evidence that the presence of depression worsens the course of heart disease. Multiple physiological processes have been hypothesized to underlie this apparent connection. These include decreased endothelial nitric oxide, platelet activation, and reduced heart-rate variance. Each one of these is a reaction that may be helpful following tissue injury. This article surveys new research regarding these mechanisms. Recent studies also suggest that treatment of depression may influence cardiac risk factors and disease outcome. Depression may activate biological adaptations that are helpful in crisis but harmful to health in the long term.

Introduction

An association between the occurrence of depression and the occurrence of cardiac disease has been suspected for many decades. Only recently have well-designed studies demonstrated this association clearly. Depression has emerged as an important independent risk factor for heart disease, even after adjustment for other risk factors, such as smoking or obesity, that may be associated with depression. Of particular note, in some studies, heart disease presents many years after the detection of depression. The presence of depression also appears to worsen the course of existing heart disease, although evidence suggesting this is not as compelling.

This review discusses the status of research regarding the impact of depression on heart disease. Multiple mechanisms have been proposed to mediate a causal impact of depression on cardiac disease. These include the effects of depression on health-related behaviors and compliance, the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system, clotting and platelet function, inflammatory mediators, lipid metabolism, and other physiological parameters. This article focuses on three mechanisms: the nitric oxide (NO) system, platelet activation, and autonomic function as reflected in heart-rate variability, each a physiological adaptation that might be appropriate in hemorrhage and injury. It also summarizes some new results from a growing literature that treatment of depression may affect the course of cardiac disease, an area of research that may have important and direct effects on human health.

Depression and Heart Disease

Many studies have found that major depressive disorder (MDD) occurs with increased frequency in coronary artery disease (CAD). The prevalence of MDD in systematic studies is approximately 2% to 4% in the community, and approximately 10% to 14% in hospitalized medical patients.[1,2] Schleifer and colleagues[3] found an 18% incidence of MDD in patients hospitalized for myocardial infarction (MI) using systematic evaluation with *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III)*,[4] criteria, with an additional 27% of patients having minor depression.[3] Of patients with MDD, 77% still met criteria for MDD 3–4 months later. Other studies using systematic diagnostic instruments in patients hospitalized for CAD have estimated an incidence of approximately 15% to 20%.[5-7] Among patients hospitalized for unstable angina, MDD was diagnosed in 15%.[8] Of patients discharged following coronary artery bypass surgery, 20% met *DSM-IV*[9] criteria for MDD.[10] Clearly, depression is common in CAD.

MDD might result from the psychological stress of cardiac disease. There has, however, been evidence for some time that depression itself has adverse effects on cardiovascular disease, as noted by Glassman and Shapiro[7] in an important review. Malzberg[11] drew attention to the connection between MDD and CAD in his 1934 study of depressed patients admitted to the New York State Hospital system. He found the age-standardized death rate due to "diseases of the heart" for manic-depressive psychosis was approximately six times that of the general population of New York. He subsequently published another study[12] that emphasized that the death rates due to cardiac disease were even higher in involutional melancholia (approximately eight times higher than in the general population). Involutional melancholia was considered to be depression beginning in mid-life or later, frequently with agitation and nihilistic or psychosomatic preoccupations. No comparable increase occurred in other functional psychoses, such as dementia praecox. In 1969, Dreyfuss and colleagues[13] made similar observations among psychiatric inpatients in Israel: the rate of MI was about six times higher among inpatients with depression than among all other inpatients.

More systematic studies have reproduced this association. For example, Weeke and colleagues[14] used the Danish National Registry to follow patients being treated for MDD and bipolar disorder to determine the cause of death. There was a >50% increase in death due to cardiovascular disease compared to the general Danish population. While most other follow-up studies of psychiatric patients showed an association of MDD and CAD, all of this data concerned individuals with psychiatric disease who may have been at higher risk due to other factors than depression, such as smoking, obesity, or antidepressant treatment.

Prospective epidemiologic studies that control for smoking and other risk factors address the confounding factors in the above studies. In one pivotal study, Anda and colleagues[15] used data from the National Health and Nutritional Epidemiological Study to follow 2,832 patients without ischemic heart disease or serious medical illness for an average of 12.5 years. After controlling for risk factors, the relative risk of fatal CAD was 1.5 for patients with depressed affect compared to those without, and 1.6 for the incidence of nonfatal CAD. In a striking study, Ford and colleagues[16] followed 1,190 male medical students enrolled between 1948 and 1964 at Johns Hopkins University for a median of 37 years, using annual questionnaires. Reports of clinical depression, including treatment, were reviewed and confirmed by five physicians blinded to the study design. Ford and colleagues[16] found a cumulative incidence of depression of 12%, excluding depression lasting <2 weeks or reactions related to acute grief. The men with clinical depression had a relative risk for MI approximately twice that of subjects without depression, after controlling for smoking and other risk factors.

Multiple community survey studies have come to similar findings. Wulsin and Singal[17] recently reviewed 10 studies meeting their methodological criteria: 9 of the 10 studies indicated a significantly increased risk of CAD in patients with depression, while 1 study indicated a small but not significant increase. They noted that two studies that used a structured diagnostic interview showed higher risk rates than studies using self-report instruments. Their meta-analysis indicated a relative risk rate of 1.64 for CAD due to depression. Similarly, Rugulies[18] estimated the same relative risk in a meta-analysis of 11 studies. Even after controlling for smoking and other risk factors for heart disease, the current literature suggests that depression predisposes to the development of cardiac disease. This correlation is all the more impressive, as most of these studies have demonstrated the onset of CAD years after the baseline observation of depression.

Moreover, the presence of depression appears to worsen the course of CAD. In 1988, Carney and colleagues[5] published a follow-up study of 52 patients undergoing cardiac catheterization for CAD. The presence of depression was found to be the strongest predictor of future cardiac events, with depressed subjects more than twice as likely to develop serious complications in the ensuing year. A further prospective study came from the Montreal Heart Institute by Frasure-Smith and colleagues[6,19]: modified *DSM-III-R*[20] criteria for MDD and the Beck Depression Inventory (BDI) were assessed in 222 patients hospitalized for MI. At 6 months, the presence of MDD significantly predicted death due to CAD, with a relative risk of 3.4, after controlling for other risk factors and severity of CAD. The effect of MDD was greatest in the first 6 months. Even at

18 months, elevated BDI scores significantly predicted death, after controlling for other risk factors. Lesperance and colleagues[21] further studied 896 patients with depression measured by BDI after MI. At 5 years, the relative risk was more than three times greater for those with a post-MI BDI score >18 compared to those with a BDI <5, after adjustment for other predictive factors. The same group[8] conducted a similar study involving 430 patients admitted for unstable angina with depression measured by BDI score. A score >9 was associated with a relative risk of 6.7, even after controlling for multiple other prognostic factors.

Multiple studies in other patient groups have also found that depression worsens the course and increases the lethality of CAD.[10,22,23] However, not all studies have agreed.[24] Lane and colleagues[25] have contributed an important caution: it is reasonable to expect that patients with more severe cardiac disease might be more depressed. Studies have attempted to control for disease severity by various means. If measures of medical severity are not adequate, it might appear that depression is an independent risk factor when in fact it is not. Other authors have argued that disease severity has been adequately controlled.[23] New studies with increasingly powerful designs will contribute to this area.

Depression might affect cardiovascular disease through psychosocial mechanisms, including its effect on exercise, smoking, compliance, and other health behaviors; or through physiological mechanisms, including its effects on the autonomic system, the HPA axis, platelet function, lipid metabolism, and inflammatory mediators, such as cytokines. The connection between depression and heart disease is the subject of a large and rapidly growing literature, and a full survey is beyond the scope of this review. Finkel[26] has speculated that depression may increase cardiovascular mortality because it produces physiologic changes that are adaptive for survival following tissue injury, but are maladaptive for long-term survival. These include decreased endothelial NO, increased platelet activation, and altered sympathetic-parasympathetic autonomic balance. Each of these might improve response to acute hemorrhage but worsen chronic cardiac disease. This selective review will address the literature supporting such a hypothesis.

Nitric Oxide and Depression

NO plays a vital role in regulating cardiovascular functioning through the stimulation of soluble guanylyl cyclase.[27] This enzyme promotes vasodilation, inhibits platelet adhesion and aggregation, and curtails vascular smooth muscle proliferation and migration to inflamed endothelium. Reduced endothelial NO could promote cardiovascular disease and the threat of vascular occlusive events. NO is rapidly metabolized to nitrite and nitrate ions and is difficult to measure directly. These ions, collectively abbreviated NO_X, are more stable and can serve as a marker of NO turnover. Several known CAD risk factors, such as hypertension[28] or smoking,[29] are associated with reduced NO_X levels. However, it is still to be determined whether depression, like other known risk factors, lowers NO levels.

Chrapko and colleagues[30] approached this problem by measuring plasma NO_X and endothelial NO synthetase levels in 15 patients with MDD as defined by the *DSM-IV*, compared to 16 matched controls. All were in good health, and were not smoking or taking psychotropics. Their diets for 24 hours before testing were standardized for NO_X intake. Depressed patients had significantly lower NO_X and lower platelet endothelial NO synthetase activity. The NO_X decline was greater than that seen in smokers in the study cited above.[29]

Rajagopalan and colleagues[31] studied bracial artery vasodilation in response to the sudden release of a blood pressure cuff inflated to suprasystolic pressure in depressed patients. This vasodilation is a marker for endothelial NO activity. Endothelial vasodilation in response to exogenous NO was measured using nitroglycerin. Fifteen patients with depression meeting *DSM-IV* criteria were paired with 15 normal control subjects, matched for age and gender. All were in good health with an average age of 30 and an average body mass index of 23. There were no smokers, and none were receiving psychotropics. The brachial artery change in diameter following suprasystolic pressure cuff release increased by 9.5% in normal controls versus 3.8% in the depressed group, a statistically significant difference. In contrast, both the depressed and non-depressed had similar brachial vasodilation in response to nitroglycerin, indicating a normal response in both groups to available NO. From these findings, it is reasonable to infer that the depressed group had less available endogenous endothelial NO.

Platelet Function and Depression

Increased β-thromboglobulin (BTG) in patients with CAD was noted in 1981.[32] During that year, increased platelet factor-4 (PF4) was also detected in the same population.[33] Both of these are biomarkers connected to platelet activation. A large and complex literature has since connected platelet activation with risk for cardiac disease. Because of the previously described apparent association between depression and increased cardiac mortality, Musselman and colleagues[34] hypothesized that MDD was associated with increased platelet activation. They studied 12 antidepressant-free patients with MDD and 8 normal controls. Platelet activity was assayed through flow cytometry. Platelets from depressed subjects showed increased activation at baseline, and an increased response to orthostatic challenge.

Not all studies have reproduced these findings. Lederbogen and colleagues[35] found increased platelet aggregation in response to stimulation with collagen and thrombin in 22 patients with MDD meeting *DSM-IV* criteria compared to 24 matched controls. By contrast, Maes and colleagues[36] did not find increased platelet activation induced by collagen and adenosine diphosphate (ADP) in 79 depressed patients with *DSM-IV* MDD versus 16 normal controls. It is possible that ADP does not stimulate platelet activation as collagen and fibrinogen do. In an excellent review, von Kanel[37] noted that most studies before 1996 did not show increased platelet aggregation in MDD, although most recent studies, which are frequently better controlled and use flow cytometry, have shown increased platelet activation. Comparison of platelet activation findings is confounded by small sample size, differing measurement technologies, and differing inclusion and/or exclusion criteria. Definitive studies are still required.

MDD and CAD do appear to have an additive effect on platelet aggregation. Laghrissi-Thode and colleagues[38] noted increased PF4 and BTG in 21 subjects with CAD and MDD compared to 8 subjects with CAD alone and to 17 normal subjects (presumably their study was too small to detect the effect of CAD alone on these markers). Kuijpers and colleagues[39] also described significantly elevated PF4 in 12 subjects with MDD 3 months following MI compared to 12 post-MI subjects without MDD, with a trend toward increased BTG. Subjects were matched for age, gender, and MI severity based on transaminase levels. Serebruany and colleagues[40] retrospectively assayed multiple markers of platelet activation in serum samples from three studies of post-MI patients to examine the relationship between MDD and platelet activation in patients with CAD. Post-MI subjects with MDD, post-MI subjects, subjects with acute coronary syndrome, and a group of normal subjects were all studied. The results were complex, but it is striking that the highest levels in many of the markers were seen in patients with both MDD and CAD.

Heart-Rate Variability and Depression

Traditional mathematical modeling of healthy physiologic functioning centers on the concept of homeostasis. Central to homeostasis is the maintenance of predictable rhythms (reduction of variance) based on measurements such as heart rate.[41] Havlin and colleagues[42] have challenged the role played by homeostasis in the maintenance of a healthy heart rate:

> The healthy heartbeat is generally thought to be regulated according to the classical principle of homeostasis, whereby physiologic systems operate to reduce variability and achieve an equilibrium like state. We find, however, that under normal conditions, beat-to-beat fluctuations in rate display the kind of long-range correlations typically exhibited by physical dynamical systems far from equilibrium, such as those near a critical point (entropy or disintegration).

Unpredictability and variance within parameters reflects healthy heart function.[43] Heart-rate variability is the statistical variance in the beat-to-beat intervals of the heart rhythm, and is controlled by the autonomic nervous system.

Reduced heart-rate variance (HRV) is associated with increased sympathetic tone and decreased parasympathetic tone. In a pivotal study,[44] 715 patients who were 2 weeks post-MI were followed for 4 years. HRV had a significant inverse relationship to all causes of mortality, with a hazard ratio >2. Reduced HRV correlated with death from CAD, particularly reduced power in the lowest frequency ranges. A large body of literature demonstrates that reduced HRV is associated with decreased survival post-MI, perhaps because an abnormal balance of sympathetic to parasympathetic tone predisposes to arrhythmia.

Whether depression reduces HRV was examined by Carney and colleagues,[45] who compared HRV in 19 depressed versus 19 nondepressed CAD patients matched for age, sex, and smoking status. HRV, measured as the standard deviation of normal R-R intervals, was significantly lower in the depressed patients, with and without adjustment for cardiac vessel stenosis. The group conducted a subsequent study of 307 depressed patients compared to 365 nondepressed, matched controls.[46] Electrocardiogram (EKG) monitoring for 24 hours was done ≤28 days after MI. Subjects were included in the depressed group if the BDI score was ≥10. Depression predicted reduced HRV, despite adjustment for diabetes, smoking, age, and sex; and depression severity correlated with decreased HRV.

Agelink and colleagues[47] tested the hypothesis that MDD was associated with increased heart rate along with increased sympathetic and reduced parasympathetic tone leading to reduced HRV. Thirty-two healthy patients with MDD (as defined by Hamilton Rating Scale for Depression [HAM-D] scores >25 for 2 weeks) were compared to 64 matched, nondepressed controls. At the time of EKG monitoring, none had received antidepressants for ≥6 days. HRV was studied in low, intermediate, and high frequency bands; and during rest, deep breathing, and the Valsalva maneuver. Indices of parasympathetic activity and sympathetic-parasympathetic balance were calculated. Subjects with depression showed an increased heart rate. Subjects with moderate-to-severe depression showed indices consistent with decreased parasympathetic tone and increased relative sympathetic

tone. Findings in subjects with milder depression trended in this direction without being statistically significant.

Antidepressant Treatment and Heart Disease

If depression is a risk factor for heart disease, treatment of depression should improve the course of heart disease. Some evidence exists that such treatment can improve risk factors for CAD. Paroxetine has been shown to increase NO_X in healthy nonsmoking men.[48] Lara and colleagues[48] studied 18 healthy men without any Axis I disorder who received paroxetine 20 mg for 8 weeks. At the end of the study their NO_X had significantly increased from baseline. At 6 days after completion of the study, the NO_X had reverted to the prestudy baseline.

Sertraline has been demonstrated to inhibit platelet activation even in the presence of aspirin and clopidogrel.[49] Serebruany and colleagues[49] used a subset of patients treated with sertraline (n=28) and placebo (n=36) from the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART). Many patients in both groups had received anticoagulants, aspirin, and/or clopidogel. Markers for platelet activation were significantly reduced for the sertraline group at weeks 6 and 16 after MI.

Sertraline also improved post-MI HRV recovery in patients with MDD meeting *DSM-IV-TR*[50] criteria in a double-blind, controlled, randomized study.[51] At 2 weeks post-MI, subjects were randomized to sertraline or placebo, with 12 subjects completing active treatment and 15 subjects completing placebo treatment. Both groups were compared to a nonrandomized reference group of 11 nondepressed post-MI patients, with measurements obtained from 2–22 weeks post-MI. The recovery of normal HRV in the sertraline group matched that found in the reference group. Over the same time span, there was actually a significant decline in HRV for the placebo group. Similarly, Carney and colleagues[52] used weekly cognitive-behavioral therapy (CBT) for 16 weeks to treat MDD in 30 depressed patients, compared to 22 matched cardiac patients without depression. A subset of 12 patients with severe depression, but not the set of patients with mild depression, showed significant

improvements in heart rate and one index of HRV thought to reflect chiefly parasympathetic influence. While tentative, evidence that psychological treatment can influence electrophysiological variables is reassuring.

These and other initial studies indicate that treatment for depression may reduce certain cardiac risk factors. Even if such effects on cardiac risk factors are confirmed, it will not necessarily follow that treatment for depression will reduce cardiac morbidity and mortality. Some evidence that this may actually be the case has been obtained. Sauer and colleagues[53] used a case-control study of patients with first MI to examine the impact of selective serotonin reuptake inhibitor (SSRI) use on relative risk of MI. There were 1,081 cases with first MI and 4,256 controls studied, with 223 SSRI users in both groups combined. After adjustment for multiple risk factors, the odds ratio for having an MI in subjects using an SSRI with high affinity for the serotonin transporter was 0.59 compared to nonantidepressant users, a significant effect. Use of other antidepressants did not significantly change the risk for MI.

SADHART was the first randomized, double-blind, controlled study to address safety and efficacy of an SSRI (sertraline) in the immediate post-MI period.[54] More than 11,500 acute MI patients were screened in 40 centers, providing a yield of 369 study patients meeting *DSM-IV* criteria for MDD and not taking antidepressant drugs. After a 2-week placebo wash-out period, 186 were started on sertraline 50 mg/day and 183 on placebo, with dose adjustment as needed for 24 weeks. At completion of the study the two groups showed no differences in left ventricular ejection fraction, EKG findings, or recurrent MI. There were fewer serious adverse cardiac events in the treatment group compared to the placebo group (14.5% versus 22.4%), but that finding did not reach statistical significance. Power calculations revealed that to confirm such a reduction, 4,000 post-MI subjects with MDD would be needed. The results suggest that sertraline is safe in post-MI patients. Of note, there was a significant improvement in some quality-of-life measures in the sertraline group compared to the placebo group.[55]

If depression affects heart disease, psychosocial support might affect heart disease as well. Using self-assessment methodology on 887 post-MI patients, a study by Frasure-Smith and colleagues[56] showed that very high levels of social support significantly reduced the effect of depression on mortality and predicted greater improvements in depression symptoms than expected. In this way, social support appears to provide a buffer for some of the detrimental effects of depression on CAD. In another study of post-MI individuals, the high levels of life stress and social isolation were each associated with a roughly 2-fold increase in adverse cardiac events.[57] The occurrence of high life stress and social isolation in a single individual increased the risk of subsequent adverse cardiac events 4-fold.

The Enhanced Recovery in Coronary Heart Disease (ENRICHD) study[58] examined the impact of treating post-MI patients with randomized assignment to CBT or routine follow-up over a 6-month period.[58] Subjects were included if they met modified criteria for MDD (39%), low social support (26%), or both (34%). Antidepressant treatment was considered as an addition to the CBT if HAM-D scores were >24, or if 5 weeks of treatment did not reduce the BDI by ≥50%. SSRIs were the most common antidepressant employed. After 6 months, depression severity scores were significantly more improved in the CBT treatment group as compared to usual care: as in SADHART, both treated and untreated groups showed substantial improvement. With an average follow up of 29 months, there was no difference in recurrent MI or death between the CBT and usual-treatment groups. The inclusion of subjects without MDD, the notable improvement observed without treatment, and the therapeutic effect of antidepressant treatment may have hindered detection of a benefit in medical outcome. Subjects treated with an antidepressant showed a significant reduction in recurrent MI or death (with an adjusted hazard ratio of 0.57). While subjects were not randomly assigned to antidepressant treatment, this effect is consistent with the trend noted in SADHART, and provides further evidence that antidepressant treatment may affect not only risk factors but actual outcome.

Conclusion

Substantial evidence indicates that MDD is a risk factor for the occurrence of CAD. Research to date suggests that depression is an independent risk factor, and comparable in size to other major established risk factors. A growing body of evidence appears to show that depression is a risk factor for the progression of CAD once present. A number of studies suggest that depression reduces NO function, increases platelet activation, and reduces heart-rate variability. All of these are risk factors for CAD, and could mediate the effect of depression on CAD. Available studies are small and not all in agreement. Whether such factors are related to depression or to subjects at risk for depression (ie, are state or trait variables) remains unclear. Some recent studies show that treatment of depression improves these risk factors, and hint that such treatment improves outcome of CAD. Large, well-controlled and longitudinal studies will be required to clarify these issues. Impaired NO release, increased platelet activation, and relative sympathetic autonomic dominance are examples of responses that may be advantageous following injury. Multiple other mechanisms have been hypothesized to mediate the effect of depression on CAD. Some of these, such as increased cytokine levels and HPA function, are also reactions helpful in crisis and triggered in depression. Depression may adversely affect CAD by promoting physiological responses that are useful in acute stress, but deleterious in the long term. *PP*

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