Depression: Links With Ischemic Heart Disease and Erectile Dysfunction

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This article examines the relationships among depression, ischemic heart disease, and erectile dysfunction. Depression is an independent risk factor for the development of ischemic heart disease, and depression in the post–myocardial infarction patient is associated with increased morbidity and mortality. Ischemic heart disease and erectile dysfunction are also frequently comorbid and share many common risk factors including age, hypertension, diabetes, dyslipidemia, obesity, sedentary lifestyle, and smoking. Depression and erectile dysfunction often occur together; however, the causal relation may be difficult to determine because erectile dysfunction may be a symptom of depression, social distress accompanying erectile dysfunction may precipitate depressive symptoms, or both conditions may result from a common factor such as vascular disease.

(J Clin Psychiatry 2003;64[suppl 10]:26–30)

The relationships among depression, ischemic heart disease (IHD), and erectile dysfunction are complex and multifaceted. Although in the clinical setting depression occurring in conjunction with medical illness is sometimes considered to be exclusively a psychological reaction to a severe or chronic illness, research findings suggest that a revision of this belief is warranted. Studies have established that depression increases the risk for the development of IHD, and in patients with IHD depression is associated with an increased risk for subsequent cardiac events and mortality. Common risk factors appear to predispose men to both erectile dysfunction and IHD, and erectile dysfunction often results from vascular disease. Co-occurrence of depression and erectile dysfunction is also common; however, the causal relation is often unclear. This article reviews recent findings concerning the interrelationships among depression, IHD, and erectile dysfunction.

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Support was provided by Pfizer Inc, New York, N.Y.

Dr. Roose has served as a consultant for Forest and Organon; has received grant/research support from Eli Lilly and Wyeth; has received honoraria from Forest, Organon, and Wyeth; and has been a speakers or advisory board member for Forest.

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DEPRESSION AND ISCHEMIC HEART DISEASE

Depression and Risk of Development of Ischemic Heart Disease

A number of epidemiologic studies have investigated the relationship between depression and IHD. In the Mini-Finland Health Survey, conducted between 1978 and 1981, the investigators documented a higher mean depression score and a greater prevalence of the depressive syndrome in subjects with IHD in a subanalysis of 5355 subjects aged 40 years and older.[1] In addition, when subjects were followed for up to 8 years (mean, 6.6 years), subjects who had depression at the initial screening visit were found to be significantly more likely to have died of IHD.

Increased IHD risk associated with depression was also found in a 6-year study of 4493 elderly Americans (age ≥ 65 years) who were free of IHD at baseline.[2] In this study, the presence of depressive symptoms, as determined using the Center for Epidemiological Studies-Depression scale, was found to be an independent risk factor for the development of coronary heart disease (adjusted covariates included age, race, sex, education, diabetes, hypertension, smoking status, physical activity, total cholesterol, physical inactivity, marital status, alcohol consumption, and time-dependent covariates for congestive heart failure and angina). In those with the highest mean baseline depression scores (≥ 15 of a maximum score of 30), coronary heart disease risk increased by 40%, and all-cause mortality risk increased by 60%.

Similar findings were reported for a cohort of 1190 male former medical students followed for a median of 37

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years.[3] In a multivariate analysis (adjusted for age at graduation, baseline serum cholesterol, premature parental myocardial infarction, physical activity, time-dependent smoking, incident hypertension, and incident diabetes), a 2-fold higher risk of coronary heart disease and myocardial infarction was observed for men who reported clinical depression at any time during the follow-up period.

In a review of the evidence supporting the association between IHD and depression, Musselman et al.[4] focused on studies that prospectively followed large cohorts of subjects, assessed baseline depressive symptoms or syndrome through structured clinical interviews or established rating scales, assessed baseline cardiovascular status and documented IHD risk factors, and then followed subjects over years with careful documentation of subsequent cardiac events. Findings from these studies established that either a diagnosis of major depression or the presence of depressive symptoms increases the risk of developing IHD. Most important, the increased risk associated with depression was independent of established cardiac risk factors including hypertension, hypercholesterolemia, nicotine and other substance abuse, and physical inactivity after controlling for demographic factors (age, sex, and socioeconomic status).

Comorbid Depression and Cardiovascular Outcome

In addition to being a risk factor for the development of IHD, depression that occurs concurrently with IHD is associated with increased risk of cardiac morbidity and mortality. In the first study to document the impact of comorbid depression in patients with IHD, Frasure-Smith et al.[5] assessed the impact of depression on cardiac mortality in 222 patients followed for 6 months post–myocardial infarction. A diagnosis of major depression[5] and the presence of depressive symptoms[6] were established using a modified version of the National Institute of Mental Health Diagnostic Interview Schedule for major depressive episode and the Beck Depression Inventory (BDI) given in the hospital 5 to 15 days post–myocardial infarction. Thirty-five patients (16%) met the criteria for major depressive disorder at baseline. At 6-month follow-up, 12 patients had died, all of cardiac causes; of the patients who died, 6 had major depressive disorder (17% of depressed population) and 6 did not (3% of nondepressed population). The hazard ratio for depression adjusted for other independent cardiac mortality predictors (Killip class, previous myocardial infarction) and baseline imbalances was 3.44 (95% CI = 2.25 to 4.63). Furthermore, at 18-month post–myocardial infarction follow-up, patients who had BDI scores ≥ 10 at baseline were also found to have increased cardiac mortality compared with patients with no baseline depression (BDI score < 10).[6]

Subsequently, the risk associated with comorbid depression has been studied in other populations of patients with IHD. In a study of 430 patients hospitalized for an episode of unstable angina who did not require bypass surgery, patients who had depressive symptoms (BDI score ≥ 10) had a greater likelihood (odds ratio = 4.68, 95% CI = 1.94 to 11.27; $p < .001$) of nonfatal myocardial infarction and cardiac death during 1-year follow-up compared with patients with no depression.[7] In a study of 366 patients followed for 12 months after coronary artery bypass surgery, those who met modified criteria for major depressive disorder (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria with 2-week symptom period shortened to a few days) had a higher rate of subsequent cardiac events such as angina or congestive heart failure requiring hospitalization, myocardial infarction, cardiac arrest, repeat surgery, and cardiac mortality compared with patients with no depression (risk ratio = 2.31, 95% CI = 1.17 to 4.56).[8]

Potential Physiologic Mechanisms for Cardiac Risk Associated With Depression

Depressed patients with IHD may be at greater risk for cardiac morbidity and mortality because depressed patients are more likely to engage in high-risk behaviors such as cigarette smoking and be poorly compliant with medication regimens and healthy behavioral changes during rehabilitation.[9,10] In addition to these behavioral mechanisms, several pathophysiologic mechanisms have also been proposed to explain the association between depression and cardiac events. Findings indicative of hyperactivity of the hypothalamic-pituitary-adrenocortical axis, including elevated cerebrospinal fluid corticotropin-releasing factor levels, elevated plasma cortisol concentrations, and nonsuppression of cortisol secretion in response to dexamethasone administration, have been repeatedly reported in patients with major depression.[11] In laboratory animals, central nervous system administration of corticotropin-releasing factor produces changes similar to those observed in response to stress, including increased heart rate, elevated mean arterial blood pressure, and decreased sexual behavior.[11] Hypercortisolemia is reported to induce hypertriglyceridemia, hypercholesterolemia, and hypertension,[12] and corticosteroid therapy has been associated with the development of vascular lesions.[13] Hypothalamic-pituitary-adrenocortical axis hyperactivity may, therefore, represent a pathophysiologic pathway that contributes to the association between depression and IHD.

In addition to elevated cortisol, many patients with depression also have elevated plasma and urinary catecholamine levels,[4] indicating dysregulation of the autonomic nervous system. Imbalance between sympathetic and parasympathetic tone that results in sympathetic overdrive predisposes patients with IHD to arrhythmia, ventricular fibrillation, and sudden cardiac death.[9,10] Cardiac autonomic tone can be studied using heart rate variability analysis; decreased heart rate variability indicates vulner-

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ability to arrhythmia. Heart rate variability is lower in depressed than nondepressed post–myocardial infarction patients.[14] Thus, a relative increase in sympathetic tone, reflected by decreased heart rate variability, may also be a contributing factor to the increased cardiac mortality risk in depressed post–myocardial infarction patients.

Increased catecholamine activity may also increase platelet activation and aggregation, contributing to thrombus formation.[4,15] Musselman et al.[4] observed that physically healthy patients with depression exhibited enhanced platelet activation and responsiveness compared with healthy nondepressed subjects. Enhanced platelet activation may trigger an ischemic event. Laghrissi-Thode et al.[15] assessed whether patients with depression and IHD had increased platelet activation compared with patients with IHD alone or healthy control subjects. Mean plasma levels of platelet factor 4 and β-thromboglobulin, platelet products that are released on platelet activation, were significantly higher in the depression and IHD group compared with the IHD-alone group or the control group.

Increasing evidence suggests that coronary artery disease may be a consequence of a chronic inflammatory response to endothelial injury. Although little is known about whether depression promotes or helps to maintain inflammatory processes, several studies in physically healthy adults have shown the presence of depression to be associated with higher circulating levels of interleukin-6, C-reactive protein, and tumor necrosis factor α; however, these studies did not control for potential confounders such as cigarette smoking, medications, acute infectious illnesses, and hospitalization status.[10]

ISCHEMIC HEART DISEASE AND ERECTILE DYSFUNCTION

Vascular disease resulting in penile arterial insufficiency is one of the most common causes of erectile dysfunction.[16] As a result, erectile dysfunction and IHD frequently coexist and share common risk factors such as aging, hypertension, diabetes, dyslipidemia, obesity, sedentary lifestyle, and smoking.[17–22] In the Massachusetts Male Aging Study, a community-based survey of 1290 men aged 40 to 70 years, the age-adjusted probability for complete erectile dysfunction was 4-fold higher in those with treated heart disease (39%) compared with the entire sample (9.6%).[17]

Men presenting with erectile dysfunction of presumed vascular origin who are asymptomatic for IHD may represent a population at increased risk for future cardiovascular events.[23,24] Because impeded blood flow resulting from the atherosclerotic process may initially manifest in small arteries such as those located in the penis, thereby resulting in erectile dysfunction, erectile dysfunction may be a marker for atherosclerosis elsewhere in the body. Moreover, erectile function has also been shown to significantly correlate with severity of IHD, reflected by the number of vessels occluded.[24] Consequently, even in the absence of symptoms, occult IHD should be considered in patients presenting with erectile dysfunction, and vice versa.

ERECTILE DYSFUNCTION AND DEPRESSION

In the Massachusetts Male Aging Study, men with depression (Center for Epidemiological Studies-Depression scale score ≥ 16) had a nearly 2-fold (odds ratio = 1.82, 95% CI = 1.21 to 2.73) higher likelihood of having moderate or complete erectile dysfunction compared with men with no depressive illness.[25] The causal relation between erectile dysfunction and depression can take various forms. Erectile dysfunction can be a symptom of depression; major depressive disorder is associated with decreased libido, erectile dysfunction, and decreased sexual activity.[26] Several studies have reported that depressive illness may interfere with normal erectile neurophysiology,[27,28] as evidenced by loss of nocturnal penile tumescence that is restored after treatment of depression.[28]

Alternatively, depression may occur secondary to erectile dysfunction. In some patients, the onset of erectile dysfunction is followed by high levels of depressive, somatic, and anxious symptoms.[29] In a study comparing men presenting to a urologist for erectile dysfunction, benign prostatic hyperplasia, or both conditions, men with erectile dysfunction were 2.6 times more likely to report depressive symptoms than were those with benign prostatic hyperplasia.[30]

Improvement in erectile dysfunction may be associated with improvement in depression. In a randomized trial of sildenafil citrate in men with erectile dysfunction and significant depressive symptomatology (mean baseline Hamilton Rating Scale for Depression [HAM-D] score of 17), erectile dysfunction responders, whether receiving sildenafil or placebo, had a robust decline in BDI score (mean decline of 10.7 vs. 3.7 for nonresponders) and HAM-D score (mean decline of 10.6 vs. 2.3 for nonresponders) compared with erectile dysfunction nonresponders, indicating greater improvement in depressive symptoms.[31]

Another theory about the relationship between depression and erectile dysfunction proposes that vascular disease is the common etiology that can result in either erectile dysfunction or depression. As discussed above, vascular disease is the most frequent cause of erectile dysfunction. Vascular depression is characterized as a late-onset depression (first episode after 60 years of age), which is associated with a greater burden of lesions viewed by magnetic resonance imaging in the subcortical gray matter, deep white matter, and periventricular region than are typically observed in patients with earlier-onset depression.[32] These lesions are suggestive of a

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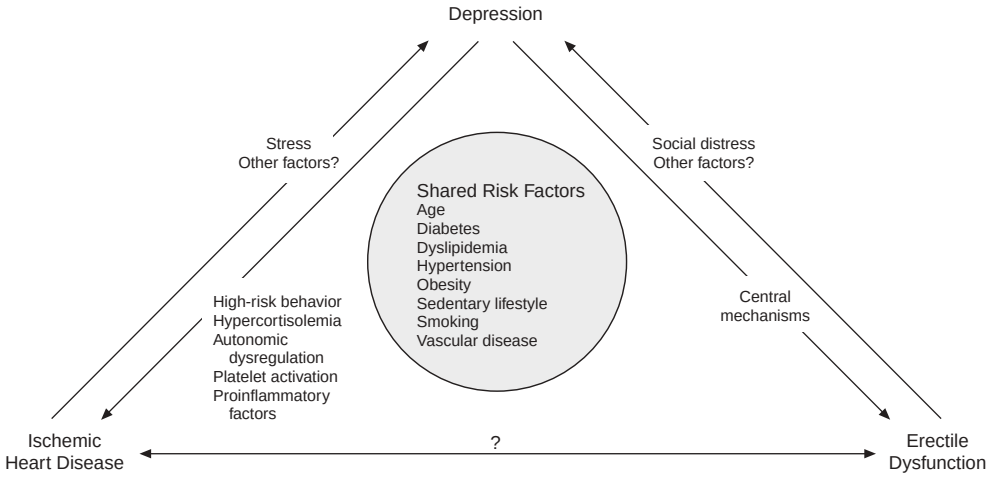
Figure 1. Interrelationships Among Depression, Ischemic Heart Disease, and Erectile Dysfunction



vascular process that may putatively result in a depressive syndrome.

CONCLUSIONS

Complex multidimensional relationships exist among depression, IHD, and erectile dysfunction (Figure 1). Depression is recognized as an independent risk factor for the development of IHD as well as a significant predictor of higher morbidity and mortality in patients with symptomatic IHD. IHD and erectile dysfunction share many common risk factors, including age, hypertension, diabetes, dyslipidemia, obesity, sedentary lifestyle, and smoking, and are also frequently comorbid. As a result, whether erectile dysfunction or IHD is the presenting condition, physicians should consider the possibility that the other condition is also present. Depression and erectile dysfunction often occur concurrently; however, the causal relation is frequently unclear because depression may cause erectile dysfunction, depressive symptoms may develop in the setting of erectile dysfunction–associated social distress, or a common factor such as vascular disease may cause both conditions.

Drug names: dexamethasone (Decadron and others), sildenafil (Viagra).

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