The Role of Depression in the Etiology of Acute Coronary Syndrome

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Recent research has confirmed that depression is a risk factor for the development and prognosis of coronary heart disease (CHD). Depressive symptoms are associated with the progression of underlying coronary atherosclerosis and clinical events such as acute coronary syndrome (ACS). Depression is poorly recognized and undertreated in patients following ACS, but progress is being made in developing abbreviated measurement tools that can be used in clinical cardiologic practice. Depressive symptoms emerging at various stages of CHD presentation may have different effects on CHD prognosis. The mechanisms mediating the relationship between depression and CHD include vascular inflammation, autonomic and endothelial dysfunction, and behavior patterns such as poor adherence to medication and advice. The optimal methods of managing depression following ACS have not yet been established.

Introduction

Coronary heart disease (CHD) currently affects nearly 16 million people in the United States, and more than one third of all deaths are the result of underlying cardiovascular disease [1]. The relationship between depression and CHD is well-established. Depression has consistently been associated with the development of the disease and with the prognosis of patients following a clinical cardiac event such as acute coronary syndrome (ACS). The disease underlying CHD is coronary atherosclerosis, a progressive condition that starts early in life and develops subclinically for decades in most individuals. Coronary atherosclerosis' etiology is multifactorial, and different factors may be influential at different stages. CHD comes to clinical attention with angina pectoris (chest pain due to failure of oxygen supply to the myocardium); an ACS, including ST elevation myocardial infarction (MI), non-ST elevation MI; unstable angina; or sudden cardiac death.

Depressive symptoms in the subclinical range and clinically diagnosed depression have been associated with CHD [2]. Despite this, a dose–response relationship has been demonstrated in some studies, with major depressive disorder (MDD) showing stronger CHD risk than subclinical depressive symptoms. Nonetheless, inconsistencies within the data remain. The use of different depression measures, outcome variables, adjustment for covariates, follow-up durations, and other factors mean that the findings are not easily comparable; future research needs to concentrate on addressing these issues.

In the past year, a number of published studies have added to the evidence relating depression to ACS. Also, several reviews have collated the evidence to date [1,3,4••,5,6]. There have been important developments in understanding the mechanisms underlying the link between depression and heart disease, examining autonomic dysfunction, inflammation, and endothelial function. In addition, health behaviors are likely to play a strong mediating role, as poor adherence to medication, smoking, and lack of exercise are associated with depression and also may contribute to CHD risk [6]. Progress also has been made in recognizing the impact of timing of depression onset and in managing depression in cardiac patients.

Etiologic Role of Depression in the Development of CHD

A meta-analysis of depression and CHD examined depression as an etiologic and prognostic indicator [4••]. A total of 21 etiologic and 34 prognostic studies published between 1966 and 2003 were identified. This paper showed that the relative risk of future CHD associated with depression was 1.81, and the risk of depression as a prognostic factor in patients with CHD was 1.80, down to 1.53 after adjustment for left ventricular ejection fraction (LVEF), a marker of disease severity. Frasure-Smith and Lesperance [3] concur in their review, arguing that more support exists for depression as an etiologic agent than in prognosis. However, these overviews highlight many deficiencies

in the literature, including inadequate adjustment for covariates, the use of a wide range of measurement tools, and variability in outcome measures.

An important issue is whether depression is associated with the progression of subclinical coronary atherosclerosis or only with the clinical manifestations of disease. A cross-sectional study by Matthews et al. [7] investigated the relationship between positive and negative psychological attributes and the level of coronary and aortic calcification in apparently healthy women. Arterial calcification is a marker of subclinical coronary artery disease and was measured using electron beam CT scans. The sample of 155 premenopausal women showed an association between depressive symptoms, measured with the Center for Epidemiological Studies Depression Scale (CES-D), and aortic—but not coronary—calcification. The sample was a homogenous set of well-educated, primarily white, healthy women, which means generalizability to other groups may be limited, and the small number of women with coronary calcification reduced the statistical power.

Another recent study investigated depression's etiologic role in the development of subclinical atherosclerosis (carotid intima-media thickness) in a prospective cohort study of healthy men and women [8•]. A range of negative emotions was assessed by questionnaire, but only depression measured by the revised Beck Depression Inventory (BDI-II) was shown to predict 3-year atherosclerosis progression. Major cardiovascular risk factors were taken into account as covariates, strengthening the findings. Depression also may influence the progression of coronary atherosclerosis in people with established CHD. A Swedish study of 102 women with CHD involved coronary angiography repeated twice over a 3-year interval [9]. After controlling for a large range of confounders, greater progression of atherosclerosis was observed in women who reported more depression and social isolation. Social integration interacted with depression so that high depression symptoms were associated with atherosclerosis progression only in socially isolated individuals.

A large-scale, retrospective cohort study investigated the risk of cardiovascular mortality in patients with severe mental illnesses, including depressive psychosis [10]. Among more than 46,000 patients with serious mental illness, death rates from CHD were increased threefold in younger patients (aged 18–49 years) and doubled in patients aged 50 to 75 years. These effects remained significant after controlling for smoking, social deprivation, and antipsychotic medication use.

Empana et al. [11] assessed the association between depression and another manifestation of CHD, out-of-hospital cardiac arrest, a clinical syndrome with similar pathology to sudden cardiac death. This population-based, case-control study of more than 2000 patients showed that the risk of cardiac arrest was doubled in patients with clinical depression after adjusting for major cardiovascular risk factors. A graded relationship was observed, with nondepressed people at the lowest risk, patients with mild depression at intermediate risk, and those with severe clinical depression at the highest risk of cardiac arrest.

Most research to date has been carried out in Western populations. However, people from the Indian subcontinent are at greater risk from CHD than other ethnic groups. The INTERHEART study, an international case-control study of patients with a first acute MI, used simple measurements of psychosocial factors to show that depression and stress were related to an increased risk of acute MI globally [12]. The population-attributable risk from psychosocial factors was similar to that of other major CHD risk factors, such as hypertension. The comparison between people from the Indian subcontinent and other nationalities showed that despite their higher incidence of CHD, South Asians had cardiovascular risk factor profiles similar to those of other ethnic groups. The earlier onset of disease in South Asians was explained by the higher levels of standard risk factors in this study.

An interesting development has been the notion that depression may act as an acute trigger of ACS. Triggers are stimuli that promote pathophysiologic reactions leading directly to the onset of acute cardiovascular disease [13]. Tofler and Muller [14] argued that emotional factors such as anger can act as triggers of ACS. Steptoe et al. [15•] investigated the circumstances surrounding the period before onset of ACS symptoms and found that the odds of suffering from ACS were significantly higher in those people who reported a moderately or severely depressed mood before the onset of symptoms. However, it is possible that recall bias and reverse causality may have influenced this association.

CHD is more common in patients of lower socioeconomic status (SES). As low SES is associated with greater psychological distress, Thurston et al. [16] hypothesized that depression and anxiety may act as mediators in the relationship between SES and CHD. They demonstrated that educational attainment (a marker of SES) has a significant graded association with CHD, that depression and anxiety were related to CHD, and that low education was associated with an increased risk of depression and anxiety. However, neither depression nor anxiety mediated the relationship between SES and CHD. This study's large, nationally representative sample and longitudinal design (an average of 15-year follow-up) added to the weight of their conclusions, although using education as the only marker for current SES may not have been appropriate in some of the population's sectors.

It is evident from this summary that recent literature has further strengthened the evidence for depression's role in the etiology of ACS, extending findings to different measures of clinical and subclinical CHD and to a broad range of sectors of the population. Nevertheless, all the evidence to date is observational, and residual

confounding is always a possibility. No intervention studies have demonstrated that ameliorating depression in otherwise healthy populations will lead to a reduction in CHD incidence.

Depression and Prognosis in Patients with CHD

Approximately 20% to 25% of patients report significant depressive symptoms following ACS [17–21]. Levels of untreated depression are very high in patients with CHD. Clinically, this is a major concern in itself and is compounded by the possibility that depression has an adverse effect on the prognosis of CHD.

Some consensus exists regarding the characteristics typical of depressed post-ACS patients. Their demographic profile appears to be similar to that of other depressed populations; for example, they are likely to be female, socially isolated, and socioeconomically disadvantaged [11,18,20,21]. Depressed post-ACS patients also are more likely to have poor biological cardiovascular risk profiles, suffer from diabetes, and have a previous history of CHD [9,11,18,20] compared with nondepressed patients. However, there is some dispute as to whether younger [18,19] or older people [11,21] are more at risk.

An analysis from the Women's Ischemia Syndrome Evaluation (WISE) prospective study of 505 patients with coronary artery disease revealed a link between depression and future mortality [20]. Patients underwent coronary angiography and were followed up for recurrent coronary events and hospitalization over an average of 5 years. There was a dose–response relationship between depression and cardiac events/mortality; people who had high BDI scores or history of depression displayed a trend toward increased risk, and those with high BDI scores and history of depression were 2.9 times more likely to suffer a cardiac event or die during follow-up.

Recent analyses by Jaffe et al. [22] of the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study examined the cardiac outcomes of post-MI patients who were clinically depressed and/or socially isolated. It was found that a range of factors, including diabetes, LVEF, and depression, were independent predictors of death and recurrent MI over 2.5 years of follow-up. Patients with moderate or severe but not mild symptoms of depression according to the BDI were more at risk.

This was supported by a study of nearly 500 patients with MI in the Netherlands, which showed that depressive symptoms assessed with the BDI predicted cardiovascular events over the next 2 years independently of type of MI, diabetes, or complications during admission [21]. The authors argued that the association with depression was weaker than that found in studies published in the 1990s, and proposed that improvements in the recognition and treatment of depression in patients with CHD may have influenced this pattern.

Another interesting analysis from the Dutch sample explored the structure of depressive symptoms in relation to cardiovascular prognosis [23••]. Somatic/affective symptoms (such as insomnia and crying) independently predicted cardiovascular death and readmissions over the 2.5-year follow-up. However, other aspects of depressive syndromes, such as cognitive/affective symptoms, did not show the same associations. These findings suggest that depression's somatic aspects are more important for cardiovascular progression. They may be related to inflammatory processes, as detailed subsequently.

Another theme of research over the past year has been the importance of depressive symptoms at different stages in the experience of ACS. This has helped to build an understanding of the impact of the stable or transient symptoms on outcome. Parashar et al. [19] examined differences among post-MI patients who had persistent depression at hospitalization and 1 month later, new depression developing only at 1 month after event, and transient depression in hospital only. They showed that of their sample of 1873 patients, 7% had persistent depression, 6% had new depression, and 13.5% had transient depression. After adjustment for baseline health status and other covariates, each category of depression was significantly associated with rehospitalization or mortality over the next 6 months. A dose–response relationship between depression severity and poorer outcomes also was observed.

De Jonge et al. [24] also differentiated between depression at different time points, comparing MI patients who had suffered depression before the MI (nonincident) and those who developed post-MI depression (incident). They found that incident depression was associated with a higher hazard ratio (HR) for recurrent cardiac events in the 12 months post-MI than nonincident depression, after controlling for confounding variables (HR 1.65, compared with 1.12). Incident and nonincident depression groups also differed in terms of personal characteristics, with nonincident depressives resembling depressives in the general population in terms of lower education and higher neuroticism. Their finding that only depression that develops post-MI is related to cardiovascular prognosis conflicts with some previous studies.

Glassman et al. [25•] recently performed secondary analyses of the Sertraline Antidepressant Heart Attack Trial (SADHART), in which 369 ACS patients with MDD were randomized into treatment and placebo groups. Depression severity was measured at 6, 10, and 16 weeks, and improvement was measured using the Clinical Global Impression-Improvement Scale. For those patients whose depression began after hospitalization, improvements in the placebo and sertraline groups were equally high. For patients whose depression began before hospitalization, the sertraline group showed greater improvements than the placebo group. This finding implies that sertraline (a selective serotonin reuptake

inhibitor [SSRI]) was most effective in those people with more persistent depression and may have little impact on patients with incident depression. The large proportion of people who reported MDD before ACS suggests that the depression in patients with ACS is not simply a consequence of their coronary disease.

One recent study found no association between mortality post-MI and depression measured over the month before MI or at 12 months post-MI [17]. The authors proposed that depression may influence heart disease prognosis through different mechanisms at different times and that the acute depressive symptoms in the period after the MI may increase CHD risk. The study also used different measures from many others, namely the Hospital Anxiety and Depression Scale (HADS) and the Schedule for Clinical Assessment in Neuropsychiatry. Methodological differences between studies make comparisons difficult. A working group on the assessment and treatment of depression in cardiovascular disease patients sponsored by the National Heart, Lung and Blood Institute (NHLBI) recommended the use of the BDI, BDI-II, the clinician-rated Inventory for Depressive Symptoms, and clinical interviews such as the Depression Interview and Structured Hamilton and the Composite International Diagnostic Interview [26].

Shortened versions of questionnaires have been designed to enable quick and easy assessment of depressive symptoms in patients who have recently experienced coronary events. Doyle et al. [27] compared the depression subscale from the HADS and the seven-item BDI fast scale (BDI-FS). The HADS depression scale classified 15% of the 598 patients with ACS as depressed, whereas the BDI-FS identified 22% as depressed. Scoring above the threshold on the HADS predicted 1-year mortality, whereas the BDI-FS did not. Huffman et al. [28] argued that two items from the BDI-II about "sadness" and "loss of interest" were simple to administer and provided a relatively effective screening tool for depression following acute cardiac events.

Other research has addressed the issue of why depression is poorly recognized in patients with CHD. Amin et al. [29•] found that ethnic minorities, those with lower education, and people with reduced LVEF were less likely to have depression recognized than other patients, although there were no differences in disease severity or hospital procedures. The authors suggested that health care providers may be to blame for the under-recognition of depression in patients with ACS because they assume that negative mood is a natural result of an ACS and thus underestimate the prognostic implications of depression. Another study compared the BDI-II (a structured clinical interview based on *DSM-IV* criteria), a psychiatrist assessment, and cardiology team assessment in recognizing clinical depression [30]. Although the study involved only a small sample, it is interesting that the poorest diagnoses came from the cardiac unit team.

Mallik et al. [18] investigated what type of patient was most likely to be depressed after an acute MI and showed that the most vulnerable group was that of women aged less than 60 years; a total of 40% were depressed according to the thresholds defined using the brief Patient Health Questionnaire. This study also showed that 73% of those reporting high depressive symptoms had not been treated for depression previously, leading the authors to conclude that depression goes largely unrecognized and untreated. However, information regarding onset of depression was not obtained; therefore, it is impossible to determine whether earlier depression had gone unrecognized or whether the depression began post-MI.

The majority of studies indicate a link between depression and poorer prognosis in patients with CHD. However, there is a need for consensus about measurement, and the widespread under-recognition of depression in CHD populations remains an important clinical problem.

Mechanisms Linking Depression and CHD

Understanding of the mechanisms linking depression with CHD has advanced rapidly in recent years. Two broad sets of processes are implicated: direct biological mechanisms, including autonomic dysfunction, neuroendocrine activation, and inflammatory responses, and behavioral or lifestyle factors, such as failure to adhere to medication regimens [5,6]. Also, it recently has been proposed that there may be shared genetic vulnerability for depression and CHD, specifically involving the inheritance of processes related to inflammation and serotonin metabolism [31].

Autonomic function

Autonomic dysfunction has been proposed as a possible mediator between depression and CHD risk, as reduced heart rate variability (HRV) and baroreceptor reflex sensitivity are associated with depression and adverse cardiovascular outcomes. A review of this literature identified 13 studies relating depression to HRV in noncardiac samples and six studies of cardiac populations [32]. Overall, depression was associated with reduced HRV, but the effect sizes were small, and there was much variation between investigations. One study of 100 patients with acute MI assessed HRV using 24-hour electrocardiogram monitoring. Depression was measured using an interview according to *DSM-IV* criteria to identify MDD, with the BDI for assessing mild to moderate depressive symptoms [33]. Depressed individuals had lower HRV and elevated heart rates compared with nondepressed patients. After controlling for standard risk factors, depression also was a significant predictor of mortality over the next 5 years. However, the addition of HRV into the regression showed that HRV was not a mediator in the relationship between depression and mortality.

By contrast, autonomic dysregulation did play a mediating role in an analysis from the ENRICHD study [34•]. This study focused on heart rate turbulence, an abnormal

heart rate response to ventricular premature contractions. Twenty-four–hour electrocardiograms were recorded from 316 depressed and 350 nondepressed survivors of acute MI. As in previous analyses, depression was associated with decreased survival during the follow-up (median 2 years). However, heart rate turbulence and very low frequency power in the HRV spectrum accounted for more than one half of the variance, thus implicating autonomic dysfunction as a mediating factor between depression and survival. Interestingly, depression was not related to survival in the first year after MI, but strongly in the second and third years, potentially implicating aggressive treatment's protective role in the first year after MI over depression's negative effects.

Inflammatory processes

An extensive literature links depression with raised levels of inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen. Reciprocal processes appear to be involved, with depression and other negative emotional states stimulating inflammatory responses, and cytokines having adverse effects on mood [35]. Inflammatory responses are associated not only with MDD but also with depressive symptoms. For example, in the Multi-Ethnic Study of Atherosclerosis (MESA), CES-D depression scores were positively associated with elevated IL-6 levels [36], whereas in a Finnish birth cohort, elevated CRP predicted a fourfold increase in the probability of recurrent depression [37]. Inflammation also is intimately involved in the etiology and progression of CHD [38].

However, the extent to which inflammatory processes mediate associations between depression and CHD is less clear. Frasure-Smith et al. [39] investigated the association between BDI-II depression, inflammatory markers, and major cardiac events over 2 years in 741 patients with ACS. Both high depressive symptoms and high CRP levels were related to increased risk of major adverse cardiac events in men, but there was little additive increase in risk in people suffering from high depressive symptoms and elevated CRP. In the Heart and Soul Study, a prospective cohort of more than 900 patients with established CHD, major depression was unexpectedly associated with lower rather than higher levels of CRP, fibrinogen, and IL-6 after controlling for confounders [40]. Carney et al. [41] have suggested that autonomic dysfunction may be related to inflammatory responses in depressed patients with CHD. In a small sample of 44 patients, fibrinogen and IL-6 both were related to reduced HRV. It is possible that disturbances in both processes are required to increase cardiac risk.

Endothelial function

The vascular endothelium plays an important role in atherosclerosis, and impaired endothelial function promotes atherogenesis and cardiovascular disease risk [42]. Broadley et al. [43•] assessed endothelial function noninvasively in depressed patients in remission and in matched controls. Depressed patients had severe endothelial dysfunction. In addition, a cortisol synthesis inhibitor, metyrapone, was administered to half of the sample. Metyrapone significantly improved endothelial function in the depressed patients, implying that excess hypothalamic-pituitary-adrenocortical function may be involved in the endothelial dysfunction observed in depression.

Behavioral pathways

Depression is associated with a range of cardiovascular risk factors related to unhealthy lifestyles, including smoking, raised cholesterol levels, adiposity, and physical inactivity [2]. Behavioral factors, notably nonadherence, may contribute to poor cardiovascular outcomes in depressed individuals following ACS. Rieckmann et al. [44] used electronic devices to monitor aspirin use in patients with ACS. Poor adherence to prescribed medication regimens was found in 10.5% of nondepressed patients, a number that rose to 42% of persistently depressed individuals over a 3-month period. In a subsequent cross-panel analysis [45], the authors found that improvements in depression over the first month following ACS led to greater medication adherence over the subsequent 2 months, strongly implicating depression as a causal factor in this relationship.

Intervention Studies

Intervention studies are essential to understand how best to manage depression in patients with ACS and improve prognosis for sufferers. In 2003, the major NHLBI-funded ENRICHD study of cognitive-behavioral therapy for post-MI patients was published and was a landmark for intervention research [46]. It failed to demonstrate favorable effects on survival of the cognitive-behavioral intervention, leading to a re-examination of the appropriate management methods [3]. One option under investigation is the combination of psychotherapy and pharmacologic treatment with SSRIs.

The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial investigated the efficacy of an SSRI, citalopram, and interpersonal psychotherapy (IPT) on 284 depressed patients with CHD in a two-by-two design. Patients received citalopram or a placebo, and either group received IPT and clinical management or clinical management alone [47••]. Citalopram emerged as an effective treatment for depressed patients with CHD, whereas IPT did not. All the patients received weekly clinical management in the form of information, advice, and encouragement for medication adherence, and this was shown to be as beneficial as 12 weeks of IPT. Therefore, the authors encourage the use of citalopram and clinical management in treating patients with CHD and major depression. Unfortunately, the study was not powered to assess cardiac end points.

Another study investigated the effects of beta-blockers on depression in patients post-MI [48]. Beta-blockers

are part of the standard cardiologic treatment program in most countries, but effects on depression have not been clearly established. In this multicenter study, there were no differences between users and nonusers of beta-blockers in the presence of depression, although there was a trend toward increased BDI scores in patients with long-term use or high dosage of the drugs. Thus, it is unlikely that beta blockade is a fruitful approach to managing mood disorder in patients with ACS.

Another study demonstrated that a cardiac rehabilitation and exercise training program for younger CHD patients (mean age 49 years) improved biological risk profiles and aerobic fitness and increased psychological well-being in terms of reduced anxiety and depression [49]. The emphasis on younger participants was an attempt to address this group's poor long-term prognosis. Unfortunately, there were no controls, so it is possible that depression would have decreased over time after the coronary event, even in the absence of the intervention.

Conclusions

Recent literature supports previous findings that depression is a risk factor for the development of and recovery from CHD. Future work should concentrate on establishing the biological and behavioral mechanisms through which this relationship operates. There are still major uncertainties about whether depression emerging after ACS has the same biological substrate and clinical significance as pre-existing depression. Unresolved issues about managing depression in cardiac patients also exist. The methodology of studies in this field is improving, with the use of larger sample sizes, more consistent measurement techniques, and appropriate statistical procedures. Treating depression in cardiac patients will not only improve their quality of life, but it may have beneficial effects on survival.

Acknowledgments

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