Assessment and treatment of depression in coronary artery disease patients

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Depressive symptoms occur frequently among patients with coronary artery disease (CAD), with prevalence estimates ranging from 15 to 30%. Risk ratios for first and recurrent cardiac events related to depression are comparable to well-established CAD risk factors and range from 2 to 7. The commonly atypical nature of depression in individuals with CAD plays an important role in the under diagnosis of depression in these patients. This review indicates that presence of atypical and subclinical depression, as well as of clinical major depressive disorders, significantly increase the risk of cardiac events. Pathophysiological mechanisms include altered autonomic nervous system activity, increased tendency toward blood coagulation, and elevated low-grade inflammation. Evidence suggests that depression in CAD patients does not reflect anatomical CAD severity or use of anti-ischemic medications. In addition to these pathophysiological pathways, depression affects CAD progression via adverse health behaviors such as smoking, poor compliance, and reduced exercise levels. Initial screening for depressive disorders can be accomplished using questionnaires, but structured clinical interviews are preferred for definite diagnosis of depression. Optimal treatment of depression in CAD generally involves both psychological and pharmacological interventions that affect both depression and its biological correlates relevant to CAD progression.

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Introduction

Depression in patients with documented coronary artery disease (CAD) is associated with elevated risks of cardiac morbidity or mortality[1-4]. Reported risk ratios range from 2 to 7, comparable to traditional cardiovascular risk factors such as hypercholesterolemia and hypertension. The biobehavioral mechanisms accounting for these negative outcomes include both biological pathways (e.g. altered sympathetic/parasym-pathetic balance) and adverse health behaviors (e.g., smoking). The symptoms used to diagnose depression are listed in table I[5]. This selective review addresses the prevalence of depressive disorders in cardiac patients, the nature and etiology of depression in CAD, assessment techniques, adverse cardiovascular consequences, and treatment options. Adequate assessment and treatment of depression will not only improve patients' quality of life, but may also promote cardiovascular health outcomes, particularly in high-risk populations.

Prevalence of depression

Prevalence estimates of depressive disorders in CAD patients range from 15 to 30%[1,2,4]. As shown in figure 1, depression is substantially more prevalent among CAD patients than in the general population: in Western industrialized countries the point prevalence varies between 2.3 and 3.5% for men and 4.5 and 9.3% for women[6]. However, depression is underdiagnosed and hence frequently untreated in CAD[7-9]. In the United States, fewer than 25% of patients are treated for their clinical depression[6]. Reasons for underdiagnosis of depression by physicians are summarized in table II[1,4,6] and include the incorrect assumption that depression has no long-lasting effects on clinical outcome and the atypical presentation of depression in many cardiac patients[1].

Table I. Symptoms for diagnosis of depressive episodes.

Depressed mood
Markedly diminished interest or pleasure in activities
Weight loss or gain (> 5%)
Insomnia or hypersomnia
Psychomotor retardation or agitation
Fatigue or loss of energy
Feelings of worthlessness or guilt
Diminished ability to concentrate or think
Recurrent thoughts of death

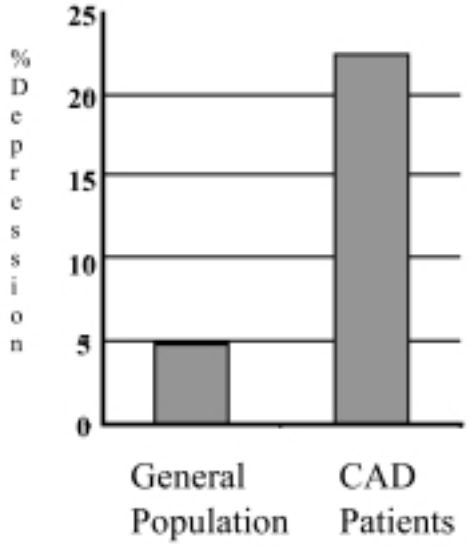

Figure 1. *Comorbidity of depression and coronary artery disease (CAD).*

Table II. Reasons for underdiagnosis of depression.

Underestimation of adverse effects on clinical cardiovascular outcome
The atypical nature of depression in cardiac patients
Depressed mood is "normal" given the patient's medical condition
Time constraints for appropriate assessment
Avoidance of social stigma associated with a diagnosis of depression
Unawareness of treatment options

The nature of depression in patients with coronary artery disease

The main categories of depressive disorders commonly observed in cardiac patients are: typical major depressive mood disorder, atypical depression, and (vital) exhaustion. In general, a depressive episode is diagnosed if one of the following primary symptoms is present (Table I): 1) depressed mood; and/or 2) markedly diminished interest or pleasure in activities, combined with other symptoms of depression (Table I; see also "assessment" section).

The symptomatology of depression in cardiac patients often differs from what is observed in psychiatric patients. Most notably, complaints of tiredness or lack of energy are more frequently observed than sad or depressed mood states[1,4,10]. Less common symptoms of depression, such as irritability and anxiety, are frequent complaints in cardiac patients and tend to occur more often than the typical feelings of guilt and low self-esteem. The atypical clinical presentation of depression is an important factor in its underdiagnosis in cardiac patients.

Research has indicated that extreme tiredness predicts adverse cardiovascular health outcomes, independent of depressed mood[11]. Based on clinical interviews, this state has been labeled "vital exhaustion"[11] and consists of extreme tiredness, increased irritability, and feelings of demoralization. The duration of exhaustion is generally several months, and complaints lasting longer than 2 years are not regarded as typical for exhaustion. Prevalence estimates of exhaustion in patients with CAD vary between 20 and 45%[1]. In a recent Italian study, 29% of 130 patients with myocardial infarction or unstable angina were classified as exhausted[12]. Elevated risks are reported for incident myocardial infarction (odds ratio-OR 2.3)[13], clinical events after coronary angioplasty (OR 2.7, 95% confidence interval-CI 1.1-6.3)[14], and sudden cardiac death (OR 2.2)[15]. As described in detail elsewhere[1], the defining features of depression and exhaustion overlap, but the etiology and biological correlates of these two constructs appear to differ.

The clinical presentation of depression (i.e., melancholic versus atypical) is related to the neurohormonal and hemostatic correlates of the disorder. Typical melancholic depression is associated with increased neuroendocrine activity, whereas atypical depression and exhaustion co-occur with hypocortisolemia[16,17]. These neurohormonal differences may in part explain why impaired fibrinolysis is observed in exhaustion but not in depression[18,19], and why cardiovascular risk factors may be differentially associated with depression versus exhaustion[20].

Etiology of depression in coronary artery disease

The causes of depression are multifactorial and include genetic predisposition, history of distressing environmental challenges, and current psychological and biological triggers. In CAD patients, both psychological and biological factors specifically related to the disease process may further contribute to the onset of depression.

The psychological antecedents of depression are not fully understood, but often include dysfunctional cognitions and/or a maladaptive response to loss of an important object or person[2,4]. Exhaustion results frequently from prolonged physical or psychological distress, over which the individual has no control[1]. At present, it is not well understood whether antecedents of atypical depression are the same as for typical melancholic depression.

The biological antecedents of depressive symptoms in CAD patients may differ from depressed individuals in general. Although it has been argued that depressive symptoms are epiphenomena of coronary disease or its pharmacological treatment, there is little support for this notion because poor left ventricular function, severity of CAD, or inducibility of ischemia

are poor predictors of depressive symptoms[1,2]. Most reports do also not support that cardiac medications are the main cause of depressive symptoms in CAD patients[21]. It is also possible that depression, its vegetative components in particular, reflect low-grade inflammation and immune activation[22] or hypothyroidism. The functional severity of CAD (e.g., exercise tolerance and severity of dyspnea) appears to be related to depressive symptoms in CAD[21]. Thus, although it cannot be ruled out that underlying coronary disease results in depressive symptoms, most evidence suggests noncardiac origins of depression in patients with CAD.

Assessment of depression and related disorders

Although depression has biological concomitants, no laboratory test is available for its diagnosis. Depressive disorders can be assessed with questionnaires and structured clinical interviews. The Diagnostic and Statistical Manual (DSM-IV) criteria for depression require presence of depressed mood and/or diminished interest, and a total of 5 out of 9 of the symptoms listed in table I for major depression, and 2 out of 9 for minor depression[5]. Symptoms have to be present most of the day, almost every day, for at least 2 weeks. In CAD patients, the 2-week criterion may be omitted for diagnosis of depression if the cardiac event occurred within a shorter time-frame[2,4].

Questionnaires. The advantage of questionnaires is their sensitivity for detecting depression and efficiency of administration. The most commonly used self-report questionnaire for depression in cardiac patients is the Beck Depression Inventory[23]. Other questionnaires have been used successfully as well, including the Zung depression scale and the Center for Epidemiological Studies Depression scale[24], among others. Most questionnaires assess mood and cognitive components (e.g., sadness, low self-esteem, guilt feelings) as well as the "vegetative" components (e.g., sleep problems, appetite changes, and lack of energy) of depression. To specifically assess exhaustion, the Maastricht Questionnaire can be used[13]. Questionnaires are sensitive screening tools for depression. However, questionnaires tend to reveal "false positives," and thus scores indicating depression require further evaluation using structured interviews.

Structured interviews. Based on the DSM criteria, structured interviews have been developed to assess depression. Among the commonly used are the Structured Clinical Interview for DSM-IV Axis I Disorders and the Diagnostic Interview Schedule[25]. A combined self-report and clinical interview technique has been designed to assess depression in patients with medical conditions (PRIME-MD)[26]. The PRIME-MD has an accuracy of 88% for the assessment of depression.

Patients with elevated questionnaire scores, but who do not fully qualify for all DSM major or minor depression criteria based on structured interview, may still suffer from atypical or subclinical depression and be at risk for adverse cardiovascular events[1,10,27].

As a consequence of the atypical nature of depression in patients with cardiac disease, a premature focus on the mood components of depression will underdetect atypical depression and may also prevent patients from disclosing their depressive symptoms. As mentioned above, some symptoms of depression such as fatigue may reflect angina equivalents. Nonetheless, these complaints should also be counted in the assessment of depression in CAD patients, because it is generally not possible to validly differentiate the underlying causes of these symptoms. Thus, to adequately assess depression in cardiac patients, it is important to ask *all* items related to depression, starting with the vegetative symptoms.

Clinical cardiovascular consequences of depression

Major depressive disorder as well as atypical and subclinical depression increase the risk of first and recurrent myocardial infarction[1,2,4,10,11,27]. Reported risk ratios vary from 2 to 7 and are thus comparable to well-established CAD risk factors such as hypercholesterolemia, hypertension, and obesity[1,2,4]. The strongest effects of depression are observed for recurrent cardiac events. This pattern of results is a consequence of the episodic nature of depressive disorders[1]. Severity of depression and extent of underlying CAD are not significantly associated[21]. Thus, depression is primarily a risk factor for clinical manifestations of CAD such as myocardial infarction and cardiovascular mortality.

Indirect cardiovascular consequences of depression are related to the adverse health behaviors and psychosocial correlates of depression. Depression is associated with increased smoking, poor compliance with medication regimens, reduced exercise levels and poor dietary habits[2,4]. Part of these adverse health behaviors result from the psychosocial consequences of depression, such as social isolation.

Treatment of depressive disorders in patients with coronary artery disease

Major depression can be effectively treated with psychological and pharmacological interventions. Atypical depression, subclinical depression, and exhaustion often require intervention as well, particularly if the patient has had prior depressive episodes or a family history of depression. The management of de-

pression has three phases: 1) the acute phase to reduce symptoms (6-12 weeks); 2) the continuation phase to prevent relapse (4-9 months); and 3) the maintenance phase for individuals with known recurrent depression (long-term treatment)[4]. Treatment of depression generally requires input from mental health professionals in the cardiac rehabilitation program.

Pharmacological interventions. Selective serotonin reuptake inhibitors (SSRI) tend to be tolerated better than the traditional tricyclic antidepressants[28]. In addition, tricyclic antidepressants can have arrhythmogenic side-effects and are thus less attractive in patients with CAD. Most SSRIs should not be used in combination with class IC antiarrhythmics and may also potentiate the effects of beta-adrenergic blocking agents. Although SSRIs reduce depressive symptoms in cardiac patients as effectively as in depressed individuals referred to psychiatry, no randomized trial has been published examining the benefits of SSRI over placebo in patients with CAD. Part of the beneficial effects of SSRI may be mediated via their effects on platelet aggregation[29].

Psychological interventions. Psychological interventions can be given on an individual basis or in groups, and may range from providing social support to more intensive cognitive-behavioral therapy. The typical duration of psychological interventions in CAD patients ranges from 8 to 12 weeks and efficacy of psychological interventions has been summarized elsewhere[30].

Cognitive behavioral therapy is often successfully used in the treatment of depressive disorders. The main goal of this approach is to modify dysfunctional thoughts and emotions by structured and empathic questioning of patients' perceptions and thought processes. Because dysfunctional cognitions play a relatively minor role in atypical depression, other treatments than cognitive-behavioral interventions may be more beneficial to CAD patients with atypical depression or exhaustion.

Evidence suggests that relaxation and breathing therapy are effective in reducing exhaustion in CAD patients. Importantly, these interventions may also successfully prevent recurrent myocardial infarction and clinical restenosis following coronary angioplasty[31,32]. At present, the efficacy of relaxation in CAD patients with depression has not been established.

Patient support groups can provide social support, reduce anxiety, and help teach patients how to effectively report symptoms and communicate with their physicians. Social isolation is a risk factor for CAD and is often a concomitant of depression. Social support from family and friends may promote treatment efficacy and patients' recovery from depression. Although patients' social networks generally respond in a supportive manner at early stages of depression, these resources can be drained as a result of the relentless demands of depressed individuals. The ongoing NIH-funded ENRICHD trial examines the effects of cognitive-behavioral therapy in a group setting for CAD patients.

Conclusions and new areas of research

Depression is far more common in CAD patients than in the general population, but often remains undiagnosed and untreated. In CAD patients, depression frequently presents as complaints of fatigue and other vegetative symptoms, rather than its typical melancholic form. Initial screening of depression can be efficiently conducted in most clinical cardiology settings; effective treatment requires involvement of a multidisciplinary team.

Some important issues require further investigation, including the following: 1) potential differences in cardiovascular consequences of atypical versus typical depression; 2) the role of the severity of depression (clinical versus subclinical) in predicting severity of adverse health outcomes; 3) validation of the differentiation between (vital) exhaustion and depression. The latter distinction may be of particular importance because depression and exhaustion have different neurohormonal correlates[16,17] and exhaustion is also one of the defining characteristics of the frailty of aging in the elderly[33].

Underdiagnosis has interfered with adequate treatment of depression in CAD patients. Factors involved in the lack of detection of depressive disorders are listed in table II and a few solutions are provided in this review. Depression can be treated effectively with a combination of psychological and pharmacological interventions. However, whether treatment of depression results in improved cardiovascular health outcomes remains to be determined. The type of treatment needs to be matched with the nature of depression and may explain why some interventions revealed unsuccessful results[34]. Depression adversely affects cardiovascular health by both biological processes and adverse health behaviors. Thus, treatment of depressive disorders in CAD will be most effective when symptom management is combined with strategies targeting both the causes as well as the biological and behavioral concomitants of depression.

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