The Role of Immune System Parameters in the Relationship Between Depression and Coronary Artery Disease

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The relationship between depressive symptoms and coronary artery disease (CAD) is mediated in part by immune system parameters. This review describes research on the psychoneuroimmunological pathways accounting for the association between depression and CAD, and addresses conceptual and methodological issues. Relationships between central nervous system correlates of depression and immune system parameters are bidirectional and are mediated via neurohormonal and parasympathetic pathways. Evidence suggests that these associations can be affected by a) the clinical characteristics of depression (e.g., typical depression versus atypical depression and exhaustion), b) the duration and severity of depressive symptoms, and c) the stage of underlying CAD. Depressive symptoms are hypothesized to affect primarily the transition from stable CAD to acute coronary syndromes via plaque activation and prothrombotic processes, and may play an additional role in the response to injury at early stages of coronary atherosclerosis. **Key words:** depression, cytokines, coronary artery disease, myocardial infarction, exhaustion, immune system, stress, risk factors.

CAD = coronary artery disease; **CRP** = C-reactive protein; **TNF-α** = tumor necrosis factor α; **IL-6** = interleukin-6; **HPA** = hypothalamic-pituitary-adrenal.

INTRODUCTION

Depression is associated with increased risk of cardiovascular morbidity and mortality (1–3). The elevated risk associated with depression is not limited to clinical major depressive disorder but also extends to subsyndromal depressive symptoms and constructs with overlapping characteristics such as vital exhaustion (4,5). Multiple pathophysiological pathways are involved in the relationship between depressive symptoms and coronary artery disease (CAD) progression and its clinical manifestations (5,6). This review addresses immune system parameters as potential biological factors involved in the relationship between depressive symptoms and CAD. Other biobehavioral pathways, discussed elsewhere in this special issue of *Psychosomatic Medicine*, include altered hypothalamic-pituitary-adrenal hormones, autonomic nervous system dysregulation, platelet dysfunction, and adverse health behaviors (e.g., smoking, poor diet, reduced exercise). The following sections provide a selective review of immune system parameters as risk factors for CAD and its clinical manifestations, the relationship between depressive symptoms and these immune system-related CAD risk factors, and the implications for future investigations in this area.

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IMMUNE SYSTEM PARAMETERS AND CORONARY DISEASE PROGRESSION

People at high risk for acute coronary syndromes can be identified based on plaque, blood, and myocardial vulnerability markers (7). These vulnerability markers are part of the atherosclerotic disease process and are often influenced by immune system parameters. Reference to immune system involvement in atherosclerosis can be found as long ago as the 19th century in descriptions by European pioneers such as Virchow and von Rokitansky. Immunological factors play a role in arterial lipid deposition and in the proliferation and migration of smooth muscle cells. In addition, immune system parameters affect gradual CAD progression indirectly by their association with known CAD risk factors (e.g., hypertension, smoking, dyslipidemia). Both direct and indirect mechanisms may initiate a vicious circle of inflammation, lipid modification, and further inflammation (7,8). The initial inflammatory response to arterial injury is generally beneficial, but the persistent presence of a damaging agent may result in continued inflammation, changing the initial restorative response to an injurious one. The subsequent walling off of the damaged area may ultimately diminish arterial function, and inflammatory processes become part of coronary disease progression (7,8). As discussed below, the biological correlates of depressive symptoms may both promote the likelihood of initial injury and adversely affect the subsequent response to vascular injury.

A complex array of immunologic factors, including multiple feedback loops, is involved in atherosclerosis, and involves macrophages, lymphocytes, cytokines, acute phase proteins, and adhesion molecules (see detailed reviews, 7–9). Among the wide range of immune system parameters, prospective epidemiologic data are most consistent for the predictive value of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) (9). A recent meta-analysis of 22 studies (7068 cardiac events) supports a significant role of CRP as predictor of incident and recurrent myocardial infarction and cardiac death (odds ratio = 1.5; 10). CRP is a nonspecific marker of systemic inflammation that activates coronary endothelium and accumulates in plaques. CRP, IL-6, and TNF-α tend to be correlated within patients, and the combined presence of elevated CRP, IL-6, and TNF-α

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in the upper tertile is associated with elevated risks of clinical manifestations of CAD (relative risk = 2.3; 95% confidence interval = 1.5–3.5) and congestive heart failure (relative risk = 4.2; 95% confidence interval = 2.5–7.0), exceeding the risks of the separate inflammatory markers (11). CRP measures are relatively stable over time (e.g., within-person correlation coefficient of CRP over 12 years = 0.59; 10). Many factors, including psychosocial cardiovascular risk factors, may influence the pathophysiological role of these inflammatory measures (see below and Figure 1).

At advanced stages of CAD, immunological processes play a role in vulnerable plaque activation and thrombus formation, thus promoting acute coronary syndromes, such as myocardial infarction (8). Plaque rupture is the most common type of atherosclerotic plaque complication, accounting for approximately 70% of all acute coronary syndromes (7). In addition to plaque activation, inflammation and blood coagulation are mutually influencing processes, further enhancing the likelihood of occlusive clot formation (12). The majority of culprit plaques leading to acute coronary syndromes are observed in nonstenotic lesions (i.e., with luminal narrowing of $<50\%$), which has important implications for biobehavioral processes involved in CAD outcomes. As shown in Figure 1, it is hypothesized that the primary immune system-related pathway explaining the association between depressive symptoms and CAD is via its effects on vulnerable plaque activation and increased risk of thrombus formation, leading to acute coronary syndromes in patients with underlying CAD.

The role of chronic infection in gradual CAD progression is supported by seroepidemiologic studies demonstrating elevated levels of antibodies to various pathogens (e.g., cytomegalovirus, *Chlamydia pneumoniae*) in patients with CAD. Evidence indicates that the likelihood of CAD increases with the number of pathogens to which an individual has been exposed (13). Microorganisms can adversely affect the coagulation/fibrinolysis balance and are most likely to act as indirect CAD promoting factors. Microorganisms activate leukocytes and cause transformation of vascular cells including endothelial and smooth muscle cells, resulting in a chronic low-grade inflammation. Thus, immune system parameters are involved in the gradual progression of CAD and play an additional important role in the onset of acute coronary syndromes.

DEPRESSIVE SYMPTOMS AS RELATED TO IMMUNE SYSTEM PARAMETERS RELEVANT TO CAD

There is overlap in the characteristic immune system correlates of depression and the immune system-related risk factors for CAD (e.g., elevated CRP levels, proinflammatory cytokines such as IL-6 and TNF-α, leukocytes, and increased antibody levels to viruses). Evidence suggests that the psychobiological pathways, including those related to the immune system, by which depression is associated with adverse CAD outcomes depend on a) the clinical characteristics of depressive symptoms (e.g., typical depression versus atypical depression and exhaustion), b) the duration and severity of depressive symptoms (major depressive disorder versus subsyndromal depressive symptoms), and c) the stage of underlying disease (5,14).

Regarding the clinical characteristics of depression, evidence indicates that in addition to depression, other indicators of psychological distress (e.g., bereavement, separation, and uncontrollable daily hassles) are associated with increased risk of CAD as well as altered immune system parameters. The immunosuppressive correlates of major depressive disorder parallel those of sustained emotional distress (15). An impressive literature exists on the immunologic correlates of depression (16) and other measures of emotional distress (15,17–19). In brief, depressive symptoms are associated with a wide range of immune system parameters, including increased numbers of peripheral leukocytes (particularly neutrophils and monocytes), decreased lymphocytes, and elevated cytokine production (e.g., IL-6) and acute phase proteins (e.g., CRP). Depressive symptoms are also associated with reduced func-

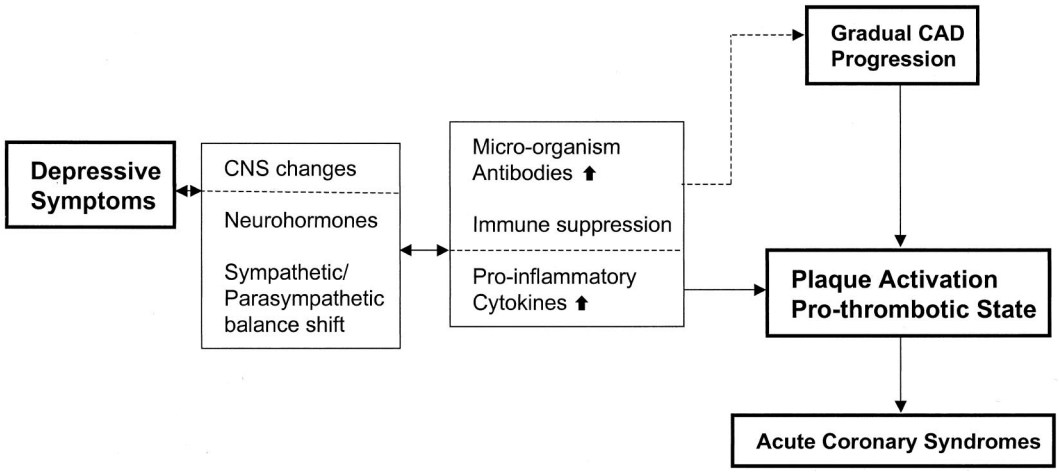

Figure 1. The relationship between central nervous system correlates of depression and immune system parameters is bidirectional, mediated by neurohormonal and parasympathetic pathways. Depressive symptoms primarily affect the transition from stable CAD to acute coronary syndromes via plaque activation and prothrombotic processes *(solid line)* and may adversely affect the initial response to injury at early stages of coronary atherosclerosis *(dashed line)*.

tional immune system measures, including lower natural killer cell activity and a decreased proliferative response of lymphocytes to mitogenic stimulation (16–18). Patients with clinical depression also have increased antibody levels of several microorganisms, including herpes viruses such as cytomegalovirus. Increased antibody titers to pathogens among people who are depressed result from an overall immunosuppressed state of the specific adaptive immunity, including reduced T-cytotoxic cells that normally suppress pathogens. The compromised adaptive specific immunity is commonly accompanied by a compensatory increase in components of the innate immune system (see also 20,21).

Increasing evidence supports that exhaustion (lack of energy, increased irritability, and demoralization) is an independent predictor of cardiovascular disease progression (5,22). Thus, there is overlap between the exhaustion construct and depression, but depressed mood and feelings of worthlessness and guilt are not characteristic of exhaustion. Gold et al. (23) have demonstrated that an atypical clinical presentation of depression (with primarily vegetative symptoms) does not coincide with hypothalamic-pituitary-adrenal (HPA) axis activation and hypercortisolemia as is commonly observed in typical depression with melancholia. Consistent with these observations is the blunted diurnal variation of salivary cortisol (24) and attenuated association of neurohormones with metabolic parameters among individuals who are exhausted (25), whereas typical depression is associated with elevated cortisol levels (23). It is not known whether the clinical presentation of depressive symptoms (i.e., typical versus atypical depression) coincides with distinct immune system characteristics relevant to cardiovascular disease progression. Our group (5,26) as well as others (e.g., 27) have consistently found elevated CRP levels among people with depressive symptoms. The association between exhaustion and CRP has been shown to remain significant after adjusting for potentially confounding variables (age, sex, race, diabetes mellitus, smoking status, systolic blood pressure), whereas the association between depressed mood and CRP is reduced when adjusting for the same variables (26). Thus, the clinical nature of depression may influence the association between depressive symptoms and immune system parameters.

Second, the duration and severity of depressive symptoms affect the biobehavioral pathways involved in CAD. Most evidence is consistent with a dose-response relationship between the severity of depression and CAD outcomes. However, depressive symptoms wax and wane over time, and biological correlates relevant to CAD progression may vary accordingly. Long-term prospective studies (>10 years) have documented elevated risk of depression for adverse CAD outcomes, but research findings nonetheless indicate that the predictive value of depression for acute coronary syndromes is strongest within the first 2 years after its assessment (4,5). This pattern of results may indicate that the duration of episodic phases of depression is not long enough to initiate and sustain the atherosclerotic process. In support of this theory is that no consistent associations have been found between depression and CAD severity (28). It is therefore hypothesized that the immune system correlates of depression are primarily involved in the transition from stable CAD to plaque activation and rupture (Figure 1).

Third, it is important to differentiate anatomical measures of CAD severity (such as severity of CAD at coronary angiography) from its major clinical manifestations as acute coronary syndromes, i.e., myocardial infarction and sudden cardiac death. It is possible that depressive episodes in young adulthood promote early vascular injury and subsequent atherosclerotic changes via immune system-related pathways. At early stages of atherosclerosis, these proinflammatory markers may promote further coronary atherosclerosis by enhancing macrophage and lipid deposition processes, thus promoting gradual CAD progression. Furthermore, at advanced CAD stages, low-grade inflammation can reduce plaque stability, and subsequently lead to acute coronary syndromes.

BIDIRECTIONALITY IN THE RELATIONSHIP BETWEEN DEPRESSION AND IMMUNE SYSTEM PARAMETERS

The relationship between depression and immune system parameters is purportedly bidirectional, such that central nervous system correlates of depressive symptoms result in immune system changes and vice versa.

The main outflow pathways by which the central nervous system affects the immune system are the HPA axis and the autonomic nervous system. Corticotropin-releasing hormone is elevated in typical depression and acts as the main regulatory hormone in the acute stress response, resulting in the release of proinflammatory cytokines as well as a wide range of other immune system responses. The autonomic nervous system also plays an important role in the acute phase reaction, and parasympathetic outflow inhibits macrophage activation via the cholinergic anti-inflammatory pathway (29). Depression is associated with decreased parasympathetic nervous system activity in CAD patients, which may thus contribute to elevations in proinflammatory cytokines.

In addition to efferent central nervous system effects on the immune system, a reverse relationship has been documented as well, such that inflammatory processes cause central nervous system responses via both humoral and neural pathways. These central nervous system changes are associated with depressive symptoms (20), although the exact mechanisms accounting for these associations require further research (21,30). Administration of proinflammatory cytokines (e.g., TNF-α) results in elevated extracellular cerebral serotonin (31) as well as depressed mood, increased sleep, and general malaise (21). Musselman et al. (32) have demonstrated that among patients treated for melanoma, depression develops in response to TNF-α administration, primarily among people who display an initial HPA response to TNF. Furthermore, this mood response could be reduced by pretreatment with paroxetine. Multiple pathways have been hypothesized for elevated cytokine levels in the brain because cytokines do not readily cross the blood-brain barrier. One pathway involves

stimulating effects of peripheral cytokines on the nucleus tractus solitarius via afferent projections of the vagus nerve to activate specific brain regions including the hypothalamus and the paraventricular nucleus (21). These observations indicate that depressive symptoms are associated with immune system parameters relevant to CAD progression, and that these associations are bidirectionally mediated via the central nervous system.

FUTURE DIRECTIONS

Future research on the role of depression and immune system involvement in CAD is needed to clarify a) the importance of subsyndromal depressive symptoms, exhaustion, and sickness behavior; b) the role of health behaviors and comorbid medical conditions; and c) the potential relevance of monitoring immune system parameters in behavioral intervention studies addressing primary and secondary cardiovascular risk. These areas are briefly addressed here.

Although there is substantial overlap between typical depression and other conditions characterized by depressive symptoms, there may be important differences in biological correlates as well as clinical outcomes related to the clinical features of depressive symptoms (5,22,23,25). The hypothesis that proinflammatory cytokines primarily affect fatigue and energy depletion and that depression will primarily develop among people in whom the immune response coincides with elevated HPA axis activity remains to be tested. Animal models of sickness behavior, induced by administration of cytokines, may provide new insights into the bidirectional relationships between immune system parameters and depressive symptomatology. Sickness behavior shares common features with depression and exhaustion and is characterized by reduced social and sexual behaviors, increased pain sensitivity, reduced activity levels, depressed mood, cognitive alterations, and decreased food and liquid intake. Thus, sickness behavior may have an adaptive function by conserving energy resources. More research is needed to establish the clinical importance of the bidirectional relationship between immune system parameters and brain function, particularly in vulnerable populations (29).

Health behaviors and comorbid conditions are important effect modifiers in the psychoneuroimmunologic aspects of cardiovascular diseases. The pattern of immunologic correlates of depression is quite complex, and at present, the relative importance of adverse health behaviors (e.g., smoking and poor diet) versus neuroendocrine and autonomic nervous system pathways is not fully understood. It will be essential carefully to assess and control for comorbid medical conditions as well as health behaviors in investigations examining the triad of immune system parameters, psychological factors, and cardiovascular disease.

In conclusion, rapid progress is continuously being made in understanding the immune system components of cardiovascular diseases. Current knowledge of proinflammatory cytokines such as IL-6 and TNF-α will be expanded to include cytokine receptors, chemokines, metalloproteases, and multiple flow cytometry-based arrays of cell expression, among others. Progress in the noninvasive assessment of coronary plaque activation levels continues, including electron beam tomography, contrast-enhanced magnetic resonance imaging, and thermography. These novel technologies will help elucidate biobehavioral processes at early and progressed stages of coronary disease, promote the development of biopsychosocial theories linking psychological factors to CAD outcomes, and optimize risk stratification. Because of the recurring nature depression and other episodic risk factors, more information is needed regarding the time trajectory of immunologic and psychological factors in patients at risk for acute coronary syndromes. It will be important to integrate methodologies from psychology, neuroscience, and immunology in cardiovascular risk assessment and intervention studies, using longitudinal as well as animal and human experimental designs.

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