The role of immune abnormality in depression and cardiovascular disease

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Abstract
Depression and cardiovascular disease (CVD) are both highly prevalent disorders, and some evidence shows that there is a ‘vicious cycle’ linking major depression and CVD. There is also growing evidence that immune abnormalities underpin the common pathophysiology of both CVD and major depression. The abnormalities include the following: abnormal levels of inflammatory markers, such as interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α) and interleukin-12 (IL-12); increased acute phase proteins, such as C-reactive protein, fibrinogen and haptoglobin; and abnormal complement factors. The findings show that major depression and CVD patients have greater immune abnormalities, which may increase depressive symptoms and cardiovascular pathological changes, and that there may be a bidirectional relationship, therefore more prospective studies are needed to draw conclusions.

Keywords: Cardiovascular disease; Depression; Immune abnormality

1 Introduction
Depression and Cardiovascular disease (CVD) are both highly prevalent disorders, and both of them can cause a notable decrease in the quality of life and increase the economic burden. Depressed patients are more likely to obtain fatal or non-fatal CVD than those who are not depressed. Over the past 30 years, evidence has accumulated to indicate that depression may be a risk factor for cardiac mortality in patients with known CVD. Although the relationship between depression and undesirable prognosis in CVD patients has been widely covered, the mechanisms underlying depression in patients with CVD remain poorly understood. Some mechanisms, such as immune abnormality, endothelial dysfunction, increased platelet activity and aggregation, autonomic nervous system dysfunction and behavioral factors, may take part in the relation between depression and poor cardiac prognosis. The aim of our review is to depict the immune abnormalities that may explain the co-occurrence of depression and CVD and the enhance risk of CVD in depression patients (Figure 1).

2 The relationship between depression and cardiovascular disorder
Over the past 30 years, evidence has accumulated to indicate that patients with CVD have a higher incidence of clinical depression. A review of 24 different researches involving 14,326 patients with myocardial infarction (MI) was conducted recently. Eight of these researches used a standardized interview for the depression diagnosis. In these 8 researches, the incidence of depression ranged from 16%–45%. The enhancing recovery in Coronary Heart Disease (CHD) (ENRICHD) study, which is the largest of these researches, examined 9279 patients and reported an incidence of 20%. The mean prevalence for all the 8 studies was 20.5%. The remaining 16 researches used a validated questionnaire or rating scale. In these 16 researches, the incidence of depression ranged from 16%–45%. The enhancing recovery in Coronary Heart Disease (CHD) (ENRICHD) study, which is the largest of these researches, examined 9279 patients and reported an incidence of 20%. The mean prevalence for all the 8 studies was 20.5%. The remaining 16 researches used a validated questionnaire or rating scale. In these 16 researches, the incidence of depression ranged from 16%–45% and the weighted prevalence was 31.1%. These incidences of depression in the MI patients are higher than the possibly conservative rate of major depression in the general population, which is approximately 5% as reported by the national co-morbidity study, 5%–10% in primary care, or 6%–14%
in other inpatient medical settings. It nears the prevalence of 20%–30% reported among the stroke patients. Furthermore, major depressive disorder (MDD) is present in about 20% of CVD patients, and this rate of MDD is 2- to 3-fold higher than in the general population. These authors declare that the effects of CVD onset on depression risk are much greater than vice versa and that the effects of depression on CVD are mostly brachychronic and related to depressive recurrence.

In CVD patients, depression is often chronic and recurrent. Depressive symptoms often continue to exist in CVD patients. In studies which examine the course of post-MI depression, depressive symptoms remain at steady levels of severity over a follow-up for one year. In addition, among CVD patients who are hospitalized for acute cardiac syndromes and who were found to meet diagnostic criteria for depressive status during or shortly after admission, nearly 50% to 70% have a history of depression that predates their cardiac events. This finding is in accord with literature that finds persistent depression in patients with stable CVD and suggests that, depression exists for months or years before a cardiac event for many patients, rather than being a temporal reaction to the event.

There is an unquestionable link between depressive symptoms and adverse cardiovascular outcomes, independent of traditional risk factors and cardiac disease severity. Many studies reported that the clinical depression can nearly double the risk of mortality and nonfatal cardiac events and that even subclinical elevations in depressive symptoms are related to a poorer prognosis in patients with established CVD. More than 20 years ago, the link between depression and cardiovascular morbidity following acute coronary syndrome (ACS) was first identified; Frasure-Smith, et al. showed that major depression was an independent risk factor for 6 months’ mortality in patients with MI. This relevance has been replicated in several studies and has also been shown in coronary artery bypass graft (CABG) surgery patients. The association with recurrent cardiac disease is apparent not only for clinical depression but also for subclinical dysphoria and elevated symptoms of depression within the normal range. In addition, depression in CVD patients is associated with poorer life quality, longer hospital stays and greater cardiac-related readmissions after MI. Greater disease progression (e.g., atherosclerosis in CABG

Figure 1. Immune abnormalities underpin the common pathophysiology of both CVD and major depression. CVD: depression and cardiovascular disease; CRP: Acute phase protein; C3: serum complement C3; IL: interleukin; TNF: tumor necrosis factor.
patients) and increased use of urgent and unscheduled care can also be seen in these patients.[11–13]

3 Immune abnormalities linking depression and CVD: inflammatory markers

Inflammatory cytokines have been associated with atherosclerotic plaque formation, progression, and rupture. Studies had found that they are major contributors to the pathogenesis of coronary artery disease (CAD), unstable angina, and MI. Furthermore, inflammation plays a key role in the pathogenesis of certain types of chronic heart failure (CHF).[14–16] Not surprisingly, inflammatory cytokines [e.g., interleukin-6 (IL-6) in CHD] can independently predict cardiovascular mortality in healthy individuals and in patients with CVD and CHF. Immune activation also has a link with depression as well as with increased numbers of circulating leukocytes and proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-2 (IL-2) and IL-6. A hypothesis is that there is a positive feedback mechanism between depression and CAD. Increased concentrations of proinflammatory cytokines influence atherosclerotic plaque progression and sickness behavior. Such sickness can lead to an inactive depressed lifestyle that further heighten the risk of CAD.[17–19]

A large number of literature supports an association among tumor necrosis factor α (TNF-α), inflammation and depression. Authors state that monitoring intracellular cytokines (such as TNF-α, and IL-1) may help to select those patients who are at an rising risk to develop future clinical CVD. Following acute coronary syndrome (ACS), immune activation and the concomitant upregulation of TNF-α is usually followed by a series of physiological, behavioral and motivational changes including fever, increased slow wave sleep, hyperalgesia, anorexia, anhedonia, disturbed mood and impaired concentration – termed the acute sickness response.[20–21] This response, which is triggered by the action of cytokines on central nervous system (CNS) targets, has been extensively studied over the past 30 years and is now understood to represent a highly conserved survival strategy that shifts the organism’s priorities toward pathogen resistance, energy preservation and recovery.[22–23] Although usually adaptive and reversible, in vulnerable individuals, the response may lead to a more sustained and severe pattern of behavioral and physiological changes typical of major depression.[24]

Existing evidence shows that interleukin-1β (IL-1β), which is increased in depression, has pro-atherogenic capacities. The pro-atherogenic effects of IL-1β are caused by increased endothelial adhesion, increased vascular permeability, activation of macrophages, smooth muscle and endothelium cell proliferation, and protease-induced plaque rupture.[25] Ma, et al.[26] recently observed that IL-1β levels were increased in the serum of patients with CAD and that severe depression was significantly increased. Next, by culturing human umbilical vein epithelial cells with the depressive CAD patient’s serum, it was found that the serum induced the activation of the IL-1β and NF-kB promoters. Moreover, the activities of these two transcription factors were blocked by atorvastatin. They also found that aspirin functioned similar to atorvastatin, compared with one of the antidepressants-sertraline.

There also have studies show that depression is also linked to increased levels of IL-6, both in patients with or without a history of CVD.[27–29] Kop, et al.[30] found that depression predicted cardiovascular mortality; controlling for IL-6 reduced the association by 12.7%, suggesting that inflammation modestly contributed to the effects of depression on CVD mortality.[30] Vaccarino, et al.[31] also found that depression predicted CVD events; inflammatory factors (IL-6) reduced this association by 20% in a study of 559 women with suspected cardiac ischemia, again suggesting some contributions to the effects of depression on cardiac events. Therefore, it appears that inflammation takes a part in the mediation of the effects of depression on CVD patients.

Another proinflammatory cytokine increasing in depression[32] and playing a role in CVD is interleukin-12 (IL-12). It was known that IL-12 can amplify T-cell accumulation within inflamed plaques.[33] Administration of IL-12 to apolipoprotein E-deficient mice can lead to increasing serum oxidized Low density lipoprotein (LDL) antibodies and accelerates atherosclerosis.[34] Study also show that functional blockade of endogenous IL-12 in mice can significantly reduce atherogenesis and improves plaque stability.[35–36] All of the above studies illustrate the role of IL-12 in atherosclerosis.

4 Acute Phase Proteins (APPs) in depression that are associated with CAD

APPs (CRP, fibrinogen, and haptoglobin) have been affirmatory associated with increased risk of CVD. Study has showed that the levels of plasma CRP increase in ACS patients and constitute an important biomarker of atherosclerosis.[37] CRP can attenuate endothelial progenitor cell survival, differentiation, and function; and CRP can induce matrix metalloproteinase-1 expression, which plays a part in plaque instability and can promote atherothrombosis.[38] Higher levels of CRP have been associated with various psychosocial factors including lower socioeconomic status, chronic work stress, caregiver strain, early life adversity,
hostility, and social isolation. There is also various evidence prompting that depression is related to rising levels of CRP, and administration of inflammatory markers can bring out symptoms of fatigue, malaise, lethargy, psychomotor retardation, irritability, and anorexia. In an analysis of data containing 6,914 men and women between the ages of 18 and 39 years from the National Health and Nutrition Examination Survey (NHANES) III, a history of MDD had strong relevance with elevated CRP.

Health, aging, and body composition study has also find elevated inflammatory markers among older individuals. In this study of older adults aged from 70 to 79 years, CRP was higher in depressed patients. Steptoe, et al. examined the relationship between inflammatory markers and acute psychological stress in a meta-analysis. The authors’ literature search 30 studies for analysis. They found that acute psychological stress was related to higher CRP. Nevertheless, it is also possible that increased inflammatory levels are associated with cardiac outcomes only after persistent elevations, so the findings following acute stress may not be the same as in longer-term studies. So Howren, et al. examined above question by studying the relation between depression and several inflammatory markers, including CRP and IL-1. The authors used meta-analysis and found a dose-dependent relationship between depression and greater levels of inflammation across both clinical and community samples, and these relationships continued after controlling for background factors and medications. The authors also found several causal relationships between depressive symptoms and inflammation by examining prospective studies. They found evidence suggesting that depression may predispose patients to greater inflammation. They also found that inflammation may increase depressive symptoms and there may be a bidirectional relationship, although the number of prospective studies available was not enough to draw conclusive results.

4.1 Fibrinogen

Fibrinogen is another acute phase reactant protein and a proinflammatory marker. Previous studies have found that elevated plasma fibrinogen were related to psychological distress and depression. The biological mechanism behind the relation between elevated fibrinogen and psychological distress and depression is still not completely understood. It is now known that fibrinogen can stimulate the synthesis of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-a from peripheral blood mononuclear cells, thus increasing the levels of proinflammatory cytokines. These proinflammatory cytokines can activate the enzyme indolamine-2, 3-dioxygenase, which degrades tryptophan into kynurenine. As tryptophan is the precursor of serotonin, decreased tryptophan concentrations can reduce serotonin synthesis, which may cause the occurrence of depression. In addition, as fibrinogen is the precursor of fibrin for the thrombi formation, it is also theoretically possible that increased fibrinogen levels could cause an increased risk of thrombus formation in vessels of the brain, which may eventually cause psychological distress and depression.

Many studies have further identified fibrinogen as a major cardiac risk factor. Fibrinogen can promote platelet aggregation and blood coagulation, increase plasma viscosity, cause the release of vasoconstrictor mediators and growth factors and lead to fibrin deposits. Moreover, fibrinogen and its metabolites can affect the vascular wall directly.

Increasing evidence suggests that there is a complex interaction among atherosclerosis, depression and fibrinogen. It has been hypothesized that a maladjusted immune system and impaired response to injury is one of the underlying mechanisms involved in the associations between psychosocial factors and the development of CAD and the progression of stable CAD to ACS. Therefore, Elderon & Whooley proposed an interconnected system that links depression, health behavior and biological changes to an increased risk of CVD and its clinical manifestations. Depression may be bilaterally related to a cluster of adverse lifestyle factors and behaviors (e.g., overweight, physical inactivity and smoking) and may consequently increase proinflammatory markers such as fibrinogen.

4.2 Haptoglobin (Hpt)

Hpt is an acute-phase plasma glycoprotein, which playing important roles in the binding of hemoglobin and protecting against heme-driven oxidative stress. According to the inflammation hypothesis in Mental disease (MD), the disease is generally related to the whole inflammatory reaction, and the depressive symptoms’ severity is positively related to inflammatory markers such as Hpt. In two separate studies, Maes, et al. found that serum Hpt levels in MD patients were higher than in the minor depression group and the control group. Other studies have also showed that major depression is consistently accompanied by an acute phase response with increased levels of acute-phase proteins such as Hpt.

The correlation between Hpt and cardiovascular disease have also been found. Matuszek et al. found a positive correlation between Hpt levels and both epicardial coronary atherosclerosis and coronary micro-circulation impairment. Patients with multivessel coronary disease and slow coronary flow were characterized by raised systemic concentrations
of Hpt. Hpt levels are significantly higher in patients with coronary disease than in controls. In addition, Hpt polymorphisms arise from variant alpha chains; however, the beta subunit is identical in all Hpt types. The beta subunit of Hpt is absent or present in low quantities in the normal intima but is abundant in fibro-fatty atherosclerotic lesions.\(^{57-58}\) Hpt containing the alpha-2 chains was associated with a higher rate of vasospasm than the Hpt alpha-1 subtype. This is of some interest because depression is associated with a higher frequency of the 2–1 subtype than the 1–1 type.\(^{59}\)

### 4.3 Complement factors

The role of complement factors in the development of major depression is a hot topic in recent years. C1QC is the first component of the classical pathway in complement activation.\(^{60}\) Jiyeong Lee, et al.\(^{61}\) detected higher plasma C1QC in major depressed patients than controls. Activation of the autoimmune system in the depressive status of MDD can upregulate C1QC. This finding would support the increased permeability hypothesis of MDD.\(^{61-63}\) Serum complement C3 (C3) is produced by activated macrophages. It acts as a cytokine\(^{64}\) and can control lipid and glucose metabolism,\(^{65}\) which can lead to CVD and diabetes. C3 is associated not only with the risk factors of CVD but also with the presence and severity of CVD.\(^{66}\) After 10 years’ observation, Stephen, et al.\(^{67}\) also found that men who are hostile and are prone to experience frequent and intense feelings of anger and depression show activation of the complement system, specifically increases in C3.

Complement factors have also been associated with the development of CVD. Increasing evidence suggests that the complement system is one of the key factors in generating and maintaining inflammation in the arterial intima.\(^{68}\) Immunostaining experiments have shown the presence of large quantity of the terminal complement complex C5-9 in association with smooth muscle cell α-actin and modified LDL.\(^{69-70}\) In vitro, lipids derived from human atherosclerotic lesions and enzymatically modified LDL can activate complement through the alternative pathway.\(^{71}\) Moreover, in rabbits deficient in the complement component serum complement C6 (C6) of the terminal complement cascade, the development of experimental atherosclerosis has been shown to be retarded. C3 and cleavage products are modified in several associated metabolic disorders including obesity, insulin resistance, type-2 diabetes, dyslipidemia, and CVD.\(^{72}\) Onat, et al.\(^{73}\) found that C3 and cleavage products are modified in cardiovascular diseases. They also found that the complement cascade is activated during myocardial ischemia and likely mediates immune and inflammatory responses in ischemic myocardium. Serum complement activation is elevated in unstable rather than stable angina pectoris which suggesting added contribution to damage extension in acute coronary syndromes. They studied whether C3 is an independent determinant of incident cardiometabolic risk (coronary heart disease, metabolic syndrome, and type 2 diabetes mellitus). The result showed that in each sex, circulating C3 can significantly predict incident CVD independent of age and smoking status. Even after entering CRP, C3 predicted CVD with a relative risk of 1.35 (95% confidence interval, 1.09–1.67) for 1-SD increments of C3 in the total sample.\(^{74}\)

### 5 Conclusion

In summary, depression and depressive symptoms are highly prevalent in patients with a range of CVD diagnoses and have been associated with poor psychiatric, functional, and cardiac outcomes, including a greater than 2-fold increase in mortality in certain populations.\(^{75}\) Further knowledge of the mechanisms mediating the link between depression and cardiac disease could help to develop treatments blocking the underlying pathophysiology that leads to worse cardiac outcomes. Several pathophysiological processes, such as immune abnormalities, hemostasis, altered metabolic and cardiac autonomic control, might play an intermediate role in the causal pathway linking depression and coronary atherosclerosis. In this review, we have shown that shared immune abnormalities underpin both depression and CVD. The abnormalities comprise the following: abnormal levels of inflammatory markers, increased acute phase proteins, and abnormal complement factors. We have proposed that immune abnormality is a common causal process responsible, in part, for both the development of depressive symptoms and for adverse cardiac outcomes, and we have drawn parallels with dysimmune-induced sickness behavior.

Although many promising mechanisms have been reviewed, direct human evidence implicated in the pathogenesis and comorbidity of depression and CVD is limited. Recent review of animal studies suggests that most of the above mechanisms are plausible; however, until we move into human experiments or trials, many future studies will be required to definitively determine which biological mechanisms are implicated in the recurrent association of depression and CVD. Future work is needed to test this pathway empirically and to elucidate the complex interactions occurring between medicine and CVD.

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Ru–Hui LIU, Jiang–Qi Pan and Xian–E TANG: manuscript writing; Bing LI: color figure; Shang–Feng LIU and Wen–Lin MA: conception and design, manuscript editing, and final approval of the manuscript.

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