Role of Depression and Inflammation in Incident Coronary Heart Disease Events

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Inflammatory biomarkers and depression have been proposed as novel coronary heart disease (CHD) risk markers. However, prospective studies have rarely assessed these 2 candidate CHD risk markers simultaneously in predicting incident CHD events. Therefore, although depression and elevated inflammatory biomarkers frequently covary, it is unclear how these risk markers relate to each other and to CHD event onset. The elucidation of these causal pathways has important clinical implications for patients who are depressed and/or have elevated inflammatory biomarkers. In this review, the publications examining the relations among depression, inflammation, and CHD events are discussed. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96:1016–1021)

Epidemiologic research has demonstrated that modifiable risk factors such as smoking, diabetes, hyperlipidemia, and hypertension are independent predictors of coronary heart disease (CHD) incidence. Because these established risk factors do not account for all patients who develop incident CHD events, novel risk markers have been proposed to better identify patients at future risk for cardiovascular events.¹ These novel risk markers must be assessed against traditional and other newly proposed risk markers to determine their independent value in predicting CHD events. Determining whether risk markers behave uniquely or redundantly in CHD risk prediction will help define their role in the causal chain to CHD events and will affect the design of future treatment trials targeting these risk markers.

Depression and Incident Coronary Heart Disease Events

Recently, extensive reports have clearly established that several behavioral and psychosocial factors increase the risk for acute coronary syndrome events independent of traditional risk factor status.² One of the best-studied factors, depression, has received considerable attention.² Prospective studies have demonstrated that depression, assessed by self-reported symptoms or by formal psychiatric evaluation, significantly predicts the risk for first CHD events, independent of established CHD risk factors, such as age, gender, smoking, hypertension, diabetes, body mass index, hyperlipidemia, and family history of CHD.³,⁴ A recent meta-analysis of prospective population studies indicates that subjects with clinical levels of depressive symptoms (relative risk 2.7, 95% confidence interval 1.6 to 4.4) or elevated depressive symptoms (relative risk 1.5, 95% confidence interval 1.2 to 1.9) are at increased risk for incident CHD events.⁵

Inflammation and Incident Coronary Heart Disease Events

Substantial advances over the past decade have demonstrated the important role of inflammation and the underlying cellular and molecular mechanisms in promoting the formation of atherosclerosis.⁶ Elevated inflammatory biomarkers have also been proposed as novel risk markers for incident CHD events.⁷,⁸ C-reactive protein (CRP) remains the most extensively investigated in clinical studies. A multitude of large epidemiologic studies have shown that CRP predicts future coronary events, independent of CHD risk factors such as age, gender, cholesterol levels, hypertension, smoking, diabetes, body mass index, and family history of CHD.⁹ The studies were consistent in their findings of an increase in relative odds of 2.0 (95% confidence interval 1.6 to 2.5) for major coronary events observed between the upper tertile and the lowest tertile of CRP levels.¹⁰ A similar significant relation has been found between incident CHD events and other candidate inflammatory biomarkers, such as interleukin-6, soluble intercellular adhesion molecule-1, and P-selectin.⁷,⁸,¹¹,¹² Similar to CRP, the prognostic significance of these circulating inflammatory molecules is not diminished by adjustment for traditional CHD risk factors.

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The Relation Between Depression and Inflammation

Because depression and inflammatory biomarkers are associated with first CHD events, it is perhaps not surprising that they appear to be associated with each other. In 4,265 men and women aged ≥65 years without a history of cardiovascular disease enrolled in the Cardiovascular Health Study, depression symptoms were significantly associated with higher levels of CRP, even after adjusting for age, gender, race, height, weight, diabetes mellitus, smoking status, and systolic blood pressure. Findings from the ATTICA study revealed that in 853 men and women without CHD, CRP, white blood cell count, and fibrinogen were independently associated with depression symptom severity. Corroborative findings from the Third National Health and Nutrition Examination Survey indicated that a lifetime history of major depression was associated with elevated CRP levels in 6,914 men and women without CHD, a finding that was much stronger in men than in women.

There is an also an association between depression and other inflammatory markers, such as interleukin-6. Thus, sufficient evidence suggests that depression and inflammation covary. However, the nature of this relation is not known, because cross-sectional data cannot discriminate among several possible explanations for the observed correlations: (1) inflammation induces depression, (2) depression induces inflammation, (3) the causal pathways are bidirectional, and (4) a third pathologic process causes depression and inflammation.

Does Inflammation Induce Depression?

Animals administered cytokines such as interleukin-1β and tumor necrosis factor-α exhibit increased sleep, reduced locomotor activity and social interactions, anorexia, reduced response to rewarding stimuli, and increased anxiety. In humans, interleukin-2 and interferon-α administration induce sleep disturbance, loss of appetite, depressed activity levels, anhedonia, and mood changes. Additionally, endotoxin injection in humans is associated with mood disturbances, including anxiety and depression. The findings of these studies strongly suggest that there is a causal pathway that leads from inflammation to depression. However, it is possible that these constellations of symptoms represent other overlapping but conceptually distinct mood disturbances, such as chronic fatigue or vital exhaustion. Further research into the various facets of mood changes exerted by cytokines should be conducted.

If depression is a consequence of inflammation, then reducing inflammation would theoretically alleviate depression. Currently, no prospective trials have assessed whether specifically targeting inflammation is associated with a reduction in depressive symptoms. If statins improve cardiovascular outcomes by attenuating inflammation, then they may also reduce depression. An observational study by Young-Xu et al showed that statin use was associated with less risk for abnormal depression scores in 761 outpatients with coronary artery disease at a mean follow-up of 4 years. The effects on depression appeared to be independent of baseline cholesterol levels and the degree of cholesterol reduction. Yang et al showed that statin use was associated with less risk for depression in a nested case-control analysis of 438 patients with newly diagnosed depression and 1,830 controls from the United Kingdom General Practice Research Database. The risk for depression in the group using statins was less than in subjects not receiving lipid-lowering therapy. Additionally, in those not receiving lipid-lowering drugs, the risk for depression was similar in hyperlipidemic versus normolipidemic subjects. These findings suggest that the lower risk for depression associated with statin use in this study was not merely a consequence of cholesterol reduction.

Not all observational studies of depression and statin therapy have had positive results. It is unclear why discrepant results exist. One explanation is that the studies with negative results enrolled patients who did not have increased levels of inflammatory biomarkers. None of the previously mentioned studies included inflammatory marker assessment. Therefore, it is unclear whether statin-induced depression reduction is more likely to be observed in patients with elevated inflammatory states, a finding that would suggest that inflammation is implicated in inducing depression. Whether other medications with anti-inflammatory properties decrease depressive symptoms is also unknown.

Does Depression Induce Inflammation?

The evidence supporting this causal direction is limited. In a cross-sectional study of 100 subjects (50 with depression and 50 without a lifetime history of psychiatric illness), CRP and interleukin-6 were found to be significantly associated with depression. Structural equation modeling indicated that depression appeared to promote weight gain, which in turn exacerbated inflammation by inducing leptin expression and increasing synthesis of inflammatory cytokines by adipose tissue. Prospective observational studies, which to our knowledge are lacking, are needed to confirm these findings.

It has been suggested that depression-induced cytokine production contributes to a hyperactive hypothalamic-pituitary-adrenal axis, triggering depression. However, there is insufficient evidence to discern between cause and effect. Finally, although not a direct assessment of depression, studies have examined the acute effect of a mental stress task on inflammatory biomarkers. Although these data are consistent with the hypothesis that a negative emotion such as depression promotes inflammatory processes, it is unclear whether a mental stress task can be equated to depression.

If the direction of causality leads from depression to inflammation, then the treatment of depression should attenuate inflammation. A decrease in cytokine levels such as interleukin-6 and interleukin-1β have been observed after...
antidepressant treatment, but not all studies have had positive results. It may be that a longer duration of depression treatment is needed before an effect on cytokine levels can be observed. Alternatively, the pleiotropic effects of antidepressants, that they directly decrease inflammation independent of their antidepressant effects, must be considered.

Other Possible Scenarios

Of course, the relation between depression and inflammation could be more complex. One possibility is a bidirectional relation in which depression exacerbates inflammation, and the presence of inflammation additionally induces further depression. Another possibility is that depression and inflammation may be consequences of another pathologic process. In this scenario, a common causal variable leads to the development of depression and inflammation and also to CHD event onset.

Relations Among Depression, Inflammation, and Incident Cardiovascular Events

In addition to the uncertainty about how depression and inflammation relate to one another, the exact relation between these risk markers and incident CHD events is not yet fully characterized. Prospective studies have rarely included depression and inflammatory biomarkers as covariates in predicting first CHD events. Thus, no definite inference can be made at this time whether these risk markers are redundant or independent in the prediction of CHD events. Depression (Figure 1), inflammatory biomarkers (Figure 2), or both (Figure 3) could lose clinical significance when considering each risk marker as a covariate. Depression and inflammatory biomarkers also could continue to significantly and meaningfully predict incident CHD events independent of each other (Figure 4). Knowledge about the independent effect or degree of redundancy between these 2 risk markers is vital to understanding their role in CHD event onset.

Implications If Depression Is No Longer Related to Coronary Heart Disease Events After Controlling for Inflammatory Biomarker Levels

The relation between depression and incident CHD events could disappear after adjusting for inflammatory biomarker levels. One possibility for these findings is that depression is the result of an elevated inflammatory state (i.e., high CRP), in which the risk for incident cardiovascular events is high.

Figure 1. Depression is no longer related to incident CHD events after adjusting for inflammatory biomarker levels. (A) Depression as an epiphenomenon. (B) Inflammation as a mediator. Solid line, causal pathway. Dotted arrow, a correlation that disappears when the other factor is considered as a covariate.

Figure 2. Inflammation is no longer related to incident CHD events after adjusting for depression level. (A) Inflammation as an epiphenomenon. (B) Depression as a mediator. Solid line, causal pathway. Dotted arrow, a correlation that disappears when the other factor is considered as a covariate.
In this model, the depression–CHD relation is spurious, and the main benefit of depression treatment would be only on the quality of life, not cardiovascular risk reduction. Another possibility is that inflammation is a more proximate mediator (Figure 1, the inflammation-mediator model) through which depression increases the risk for CHD events. Depression treatment, which would ameliorate inflammation, would lead to a reduction in CHD events. Additionally, inflammation treatment would effectively lead to a reduction in cardiovascular events. In the latter scenario, the beneficial effect of inflammation treatment on CHD events would be short term unless inflammation treatment was sustained or depression was also reduced.

Implications If Inflammatory Biomarkers Are No Longer Related to Coronary Heart Disease Events After Controlling for Depression

The relation between inflammatory biomarkers and incident CHD events could disappear after adjusting for depression level. In the inflammation-epiphenomenon model (Figure 2), inflammation is a marker of depression but is not itself directly involved in the causal chain to incident CHD events. This scenario is highly unlikely given the extensive research indicating that inflammation underlies the pathogenesis of atherosclerosis and CHD events. In the depression-mediator model (Figure 2), depression is the proximal mediator through which inflammation increases the risk for CHD events. In this case, treating and reducing inflammation would reduce depression and consequently CHD events. Treating depression directly might also be effective, but if inflammatory status remained elevated, the beneficial effect of treating depression on CHD events without treating its cause, inflammation, might be temporary unless depression treatment were sustained.

Implications If Neither Depression Nor Inflammatory Biomarkers Independently Predict Coronary Heart Disease Events When Controlling for Each Other

The relations among depression, inflammatory biomarkers, and CHD events could be due to a mutually shared factor. This would be consistent with the hypothesis that there is an unmeasured construct that leads to inflammation, depression, and CHD events (Figure 3). In this model, this third unknown factor (e.g., genetic polymorphisms) is directly responsible for the increased risk for CHD event onset, as well as for the increased inflammation and depression. However, because inflammation and depression are consequences of this factor, they are not involved in a causal link to CHD events. If this model is correct, then the treatment of depression and/or inflammation would not be efficacious in reducing cardiovascular events.

Implications If Depression and Inflammatory Biomarkers Independently Predict Coronary Heart Disease Events When Controlling for Each Other

A finding that depression and inflammation remain significant predictors for CHD events would lead one to conclude that the 2 variables are independent risk factors (Figure 4). In a recently published nested case-control study within the Prospective Epidemiological Study of Myocardial Infarction, depression and inflammatory biomarkers, including CRP, interleukin-6, soluble intercellular adhesion molecule-1, and fibrinogen, were predictors of incident CHD events after adjusting for traditional cardiovascular risk factors. After including depression and each inflammatory biomarker as covariates, the association between depression and CHD events was not diminished. Further, each inflammatory biomarker contributed significantly to CHD event risk. The use of a nonstandardized depression scale and the inclusion of only white, European men as participants were important study limitations. These findings suggest that the causal pathways through which inflammation and depres-

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sion increase the risk for CHD events may not related to each other. In this scenario, simultaneous depression and inflammation treatment would optimally reduce the risk for cardiovascular events.

Depression and Inflammation as Full versus Partial Mediators

If the association between the putative risk marker and the outcome is no longer statistically significant after adjustment for another covariate, the conclusion is generally that the proposed risk marker is no longer importantly "related" to the outcome. Under these conditions (Figures 1 and 2), the covariate may fully mediate the relation between the proposed risk marker and the outcome. However, partial mediation should also be considered. In this situation, the relation between a proposed risk marker and the outcome is no longer statistically significant after adjustment for another covariate, the conclusion is generally that the proposed risk marker is no longer importantly "related" to the outcome. Under these conditions (Figures 1 and 2), the covariate may fully mediate the relation between the proposed risk marker and the outcome. However, partial mediation should also be considered. In this situation, the relation between a proposed risk marker and the outcome still retains statistical significance, but the impact of this relation is reduced when the mediator is included. For example, if adjustment for inflammation reduces the magnitude but does not eliminate the statistical relation between depression and incident CHD events, inflammation is a partial mediator. Thus, depression may still lead to CHD events through causal pathways other than inflammation. Factors such as exaggerated platelet reactivity, abnormal blood coagulation, endothelial dysfunction, or autonomic dysfunction may be involved. The distinction between partial and full mediation may have important clinical implications, because simultaneous depression and inflammation treatment would be useful if partial mediation is present: there would be an additive benefit to treating depression and inflammation. The added complexity of partial mediation must be considered when one is evaluating the relations among depression, inflammation, and incident CHD events. Overall, understanding the pattern of causality among these risk markers and CHD events may ultimately improve strategies for CHD prevention.


