Clinical Depression and Inflammatory Risk Markers for Coronary Heart Disease

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Despite mounting evidence that psychiatric depression heightens risk for cardiac morbidity and mortality, little is known about the mechanisms responsible for this association. The present study examined the relation between depression and the expression of inflammatory risk markers implicated in the pathogenesis of coronary heart disease (CHD). One hundred adults were enrolled (68% women, 48% Caucasian, 48% African-American, mean age 30 ± 2 years). Fifty subjects met the diagnostic criteria for clinical depression; the remaining 50 were demographically matched controls with no history of psychiatric illness. All subjects were in excellent health, defined as having no acute infectious disease, chronic medical illness, or regular medication regimen aside from oral contraceptives. The depressed subjects exhibited significantly higher levels of the inflammatory markers C-reactive protein (3.5 ± 0.5 vs 2.5 ± 5 mg/L, p = 0.04) and interleukin-6 (3.0 ± 0.3 vs 1.9 ± 0.2 pg/ml, p = 0.007) compared with control subjects. Mediational analyses aimed at identifying the pathways contributing to this association revealed that neither cigarette smoking nor subclinical infection with cytomegalovirus or *Chlamydia pneumoniae* had been responsible. However, depressed subjects exhibited greater body mass than control subjects, and analyses were consistent with adiposity accounting for a portion of the relation between clinical depression and increased expression of inflammatory markers. These findings indicate that in otherwise healthy adults, depression is associated with heightened expression of inflammatory markers implicated in the pathogenesis of CHD. Increased body mass appears to be partially, although not completely, responsible for this relation. ©2002 by Excerpta Medica, Inc.

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Despite mounting evidence that psychiatric depression is a risk factor for morbidity and mortality due to coronary heart disease (CHD), little is known about the mechanisms responsible for this association.[1–6] We have advanced the hypothesis that depression promotes a mild inflammatory response by fostering maladaptive health practices (cigarette smoking, sedentary lifestyle), triggering dysregulation of hormonal systems (hypothalamic-pituitary-adrenocortical and sympathetic-adrenal-medullary axes), and increasing susceptibility to infections associated with atherosclerosis (*Chlamydia pneumoniae*, cytomegalovirus).[7] Over time this inflammatory response contributes to CHD progression by facilitating the growth of atherosclerotic plaque, precipitating the rupture of established plaque, and potentiating coagulation processes involved in thrombogenesis.[8,9] The present study attempts to test this hypothesis by examining whether depression is accompanied by differential expression of inflammatory markers implicated in CHD pathogenesis.[10–12] This study also explores the role of 3 processes that may underlie any relation between depression and inflammation—smoking, infection, and adiposity.[13,14]

METHODS

Subjects: A total of 100 adults were enrolled in the study; 50 of them met the diagnostic criteria for clinical depression, and the remaining 50 had no history of psychiatric illness. The groups were matched on a case-by-case basis with respect to age, gender, and ethnicity. All subjects were in good health, defined as having no history of chronic medical illness, no indications of acute infectious disease at study entry, as evidenced by a normal complete blood count, and no prescribed medication regimen in the past 6 months apart from oral contraceptives. Volunteers were excluded if they were >55 years old, had been pregnant in the past year, were menopausal, postmenopausal, or had irregular menstruation, were undernourished as evidenced by serum levels of albumin ≤3.3 g/dl, or reported abusing illicit drugs and/or prescription medications.

Subjects with depression were recruited through advertisements in local newspapers. To enroll in the study, subjects had to meet the diagnostic criteria for a current major depressive disorder (n = 32) or minor depressive disorder (n = 18).[15] Diagnoses were made by trained interviewers utilizing the Depression Interview and Structured Hamilton Interview.[16] Subjects with comorbid psychotic, eating, substance, or anxiety disorders (other than generalized anxiety disorder) were excluded using modules taken from the Diag-

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nostic Interview Schedule and Primary Care Evaluation of Mental Disorders.[17,18] Control subjects were also recruited through advertisements. To be eligible for the study, controls had to match a depressed subject in terms of demographic characteristics, and show a history free of psychiatric illness during the interviews.

Procedures: Potential subjects attended an initial laboratory session. After written informed consent had been obtained, subjects underwent a structured psychiatric interview to determine their eligibility. Afterward, eligible subjects were interviewed regarding their medical history, completed a battery of questions about their health practices, and had their height, weight, and waist-to-hip ratio measured. Subjects were then seated in a comfortable chair and had 3 blood pressure readings spaced 2 minutes apart. The readings were collected by an automated oscillometric device (Dinamap Pro 100, Critikon Corporation, Tampa, Florida). A 35-ml blood sample was then drawn by antecubital venipuncture. After the blood had been centrifuged for 25 minutes at 1,000*g*, the serum was aspirated, divided into aliquots, and frozen at −70°C until the end of the study. To minimize random measurement error, all subjects returned for a follow-up session 1 week later, during which time study variables (other than depression status) were reassessed in an identical fashion. To control for diurnal variation, all blood draws were performed during the early morning hours. These procedures were approved by Washington University's Institutional Review Board.

Inflammatory markers: Concentrations of interleukin-1β, interleukin-6, tumor necrosis factor-α, and monocyte chemotactic protein-1 were measured using commercially available, high-sensitivity enzyme-linked immunoadsorbent assays (R&D Systems, Minneapolis, Minnesota). C-reactive protein (CRP) was measured using high-sensitivity immunoassay on a BN-100 nephelometer (Dade-Behring, Deerfield, Illinois). Intra-assay coefficients of variation ranged from 5% to 15%. To evaluate temporal stability of the inflammatory markers, Spearman's rank–order correlations were computed between values from the 2 blood draws. The markers were moderately stable over time, with r_s values ranging from 0.60 to 0.88 for all markers except interleukin-1β ($r_s = 0.23$). The poor stability of this marker may have been the result of the low levels found in our sample; 27% of subjects had values below the assay's detection threshold. For statistical analyses, these subjects were assigned the assay's threshold value of 0.125 pg/ml.

Latent and/or chronic infectious processes: To evaluate the presence of latent and/or chronic infections that may elicit inflammation, we used commercially available enzyme-linked immunoadsorbent assay systems to measure immunoglobulin G antibodies to cytomegalovirus (Wampole Laboratories, Cranbury, New Jersey) and immunoglobulin A antibodies to *Chlamydia pneumoniae* (Savyon Diagnostics, Ashdod, Israel). The intra-assay coefficients of variation were 7% and 12%. Subjects displaying values ≥1 BU (cytomegalovirus) or ≥10 BU (*Chlamydia pneumoniae*) during both laboratory sessions were categorized as having recently active infections. Categorization as seropositive versus seronegative was consistent across the 2 blood draws in 95% of cases for cytomegalovirus and in 84% for *Chlamydia pneumoniae*.

Smoking and adiposity: Subjects who reported the daily use of cigarettes were classified as regular smokers. To measure adiposity, subjects' height and weight were assessed during each session using a balance-beam scale (Seca Corporation, Columbia, Maryland). Body mass index (BMI) was then computed as weight in kilograms divided by height in square meters. Waist-to-hip ratio was assessed to provide an estimate of abdominal adiposity. Waist circumference was measured at the midpoint between the upper iliac crest and lower costal margin at the midaxillary line, and hip circumference at the maximum width of the buttocks. The correlation between values from the 2 sessions was 0.98 for BMI and 0.85 for waist-to-hip ratio.

Other laboratory measures: A complete blood count and differential was performed to screen for acute infectious disease (Beckman Coulter, Fullerton, California). Gross nutritional status was evaluated by measuring serum albumin with spectrophotometry (Kyowa Medex, Shizuoka, Japan). Total serum cholesterol was assessed using enzymatic methods on a Hitachi 747 instrument (Kyowa Medex).

Statistical analysis: To improve the distributional properties of inflammatory markers, all values were transformed to log 10 before statistical analysis. A series of 1-way analyses of variance were then performed comparing depressed and control subjects with respect to each inflammatory marker. Because these markers showed high levels of stability over time, analyses were performed on aggregate indexes created by averaging values across the blood draws. This procedure diminishes random error and by doing so boosts statistical power. To identify pathways through which depression may become associated with inflammatory markers, the groups were compared on smoking, infection, and adiposity using analysis of variance for continuous outcomes and Pearson's chi-square for categorical outcomes. When depressed and control subjects differed with respect to 1 of these pathways, analyses of variance comparing groups on inflammatory markers were reconducted, this time statistically controlling for the variable representing the pathway. Following standard methods, we inferred support for a mediational hypothesis when this procedure significantly attenuated observed group differences on an inflammatory marker.[19] All statistical analyses were based on tests of significance with $\alpha = 0.05$. Data are presented as mean ± SD unless otherwise noted.

RESULTS

Depressed and control subjects were very similar with respect to demographic features and cardiovascular risk factors (Table 1). The only exception to this was weight; depressed subjects weighed significantly more than controls ($F [1, 98] = 6.84$, $p < 0.01$).

TABLE 1 Characteristics of Sample Subjects

	Depressed (n = 50)	Control (n = 50)
Age (yrs)	30 ± 10	30 ± 10
Women	34 (68%)	34 (68%)
Caucasians	22 (44%)	22 (44%)
African-Americans	24 (48%)	24 (48%)
High school graduates	46 (92%)	50 (100%)
Married	7 (14%)	11 (22%)
Height (m)	1.7 ± 0.1	1.6 ± 0.1
Height (in)	66 ± 3	66 ± 4
Weight (kg)*	84 ± 23	73 ± 18
Weight (lb)*	187 ± 51	163 ± 40
Oral contraceptive users	5 (10%)	11 (22%)
Systolic blood pressure (mm Hg)	113 ± 11	114 ± 15
Diastolic blood pressure (mm Hg)	71 ± 8	68 ± 10
Heart rate (beats/min)	68 ± 9	68 ± 11
Total cholesterol (mg/dl)	178 ± 32	180 ± 37
First-degree relative with premature CHD	9 (18%)	8 (16%)

Values are expressed as mean ± SD.
*Depressed and control subjects differ at $p < 0.01$.

Clinical depression and inflammatory markers: Subjects with depression exhibited significantly higher concentrations of CRP ($F [1, 98] = 4.58$, $p < 0.04$) and interleukin-6 ($F [1, 98] = 7.64$, $p < 0.007$) compared with control subjects (Figure 1). There were no significant differences between the groups on monocyte chemotactic protein-1 or tumor necrosis factor-α ($p > 0.23$). In terms of interleukin-1β, control subjects had significantly higher levels compared with subjects with depression ($F [1, 98] = 8.11$, $p < 0.006$). These differences persisted after statistical adjustment for the demographic characteristics and cardiovascular risk factors listed in Table 1 (all p values ≤ 0.05).

To determine whether there were "dose–response" relations between the severity of depressive symptoms and the levels of inflammatory markers, Pearson correlations were computed between clinical ratings on the Hamilton Depression Scale and the inflammatory outcomes. Across the entire sample, more severe depressive symptoms were associated with marginally higher levels of CRP ($r = 0.17$, $p < 0.08$) and tumor necrosis factor-α ($r = 0.18$, $p < 0.07$), significantly higher interleukin-6 ($r = 0.26$, $p < 0.01$), and significantly lower interleukin-1β ($r = -0.26$, $p < 0.009$). These findings suggest that a weak dose–response relation exists between the severity of depressive symptoms and the expression of inflammatory markers.

Contribution of smoking: Subjects with depression were significantly more likely to be regular smokers than control subjects (34% vs 4%; chi-square 14.62, $p < 0.001$). However, statistically adjusting for various indexes of smoking status (packs/day × years of smoking) did not attenuate group differences on inflammatory markers (p remained < 0.06), suggesting that smoking was not the mechanism responsible for the higher levels of CRP and interleukin-6, and lower levels of interleukin-1β observed in subjects with depression.

Contribution of latent and/or chronic infections: The proportion of subjects who were seropositive for antibody titers to the pathogens was similar in the depressed and control groups (cytomegalovirus 42% vs 52%, *Chlamydia pneumoniae* 26% vs 32%; $p > 0.40$). When antibody titers were treated as continuous variables, similar patterns of null results emerged from analyses ($p > 0.70$). These findings suggest that cytomegalovirus and *Chlamydia pneumoniae* were not responsible for the group disparities with respect to inflammatory marker expression.

Contribution of adiposity: Depressed subjects had a significantly greater BMI compared with control subjects (30.5 ± 8.5 vs 25.9 ± 5.2 kg/m^2; $F [1, 98] = 10.47$, $p < 0.003$). Across the entire sample, BMI was positively related to levels of CRP ($r = 0.62$, $p < 0.001$) and interleukin-6 ($r = 0.63$, $p < 0.001$), but unrelated to interleukin-1β ($r = -0.16$, $p > 0.12$). When relations between depression and inflammation were adjusted for BMI, group differences in CRP ($F [1, 97] = 0.06$, $p = 0.81$) and interleukin-6 ($F [1, 97] = 0.98$, $p = 0.33$) were attenuated. With BMI in the equation, the amount of variance that depression accounted for decreased from 4% to <1% for CRP and 7% to 1% for interleukin-6. These represent statistically significant decreases when using the Sobel test (for CRP $z = 2.08$, $p < 0.04$; for interleukin-6 $z = 2.60$, $p < 0.001$). Notably, BMI remained a significant predictor of CRP ($F [1, 97] = 53.73$, $p < 0.0001$) and interleukin-6 ($F [1, 97] = 52.77$, $p < 0.0001$) under these circumstances. Controlling for BMI did not attenuate the group differences in interleukin-1β ($F [1, 97] = 6.11$, $p < 0.02$).

To determine whether depression had a relation with inflammation that was independent of its association with adiposity, we performed further analyses stratifying subjects by diagnosis and body mass. Figure 2 shows a synergistic relation between depression and adiposity, such that subjects with depression with high body mass exhibited significantly higher levels of CRP ($F [1, 98] = 29.42$, $p < 0.001$) and interleukin-6 ($F [1, 98] = 41.45$, $p < 0.001$) compared with subject groups defined by other combinations of these factors. These findings are consistent with the hypothesis that adiposity is partially, although not completely, responsible for the elevated levels of inflammatory markers seen in subjects with depression. These findings also suggest that depression's relation with inflammation emerges most prominently in subjects with high adiposity.

A final series of analyses examined whether these findings may be attributable to central (abdominal) adiposity. Although subjects with depression exhibited significantly more central adiposity than control subjects (0.86 ± 0.08 vs 0.82 ± 0.07; $F [1, 98] = 6.58$, $p < 0.02$), adjusting for waist-to-hip ratio did not attenuate the group differences in circulating levels of CRP, interleukin-6, or interleukin-1β ($p < 0.04$). These findings suggest that whole-body adiposity, rather than fat distributed in the abdominal region, contributes to the inflammatory response in subjects with depression.

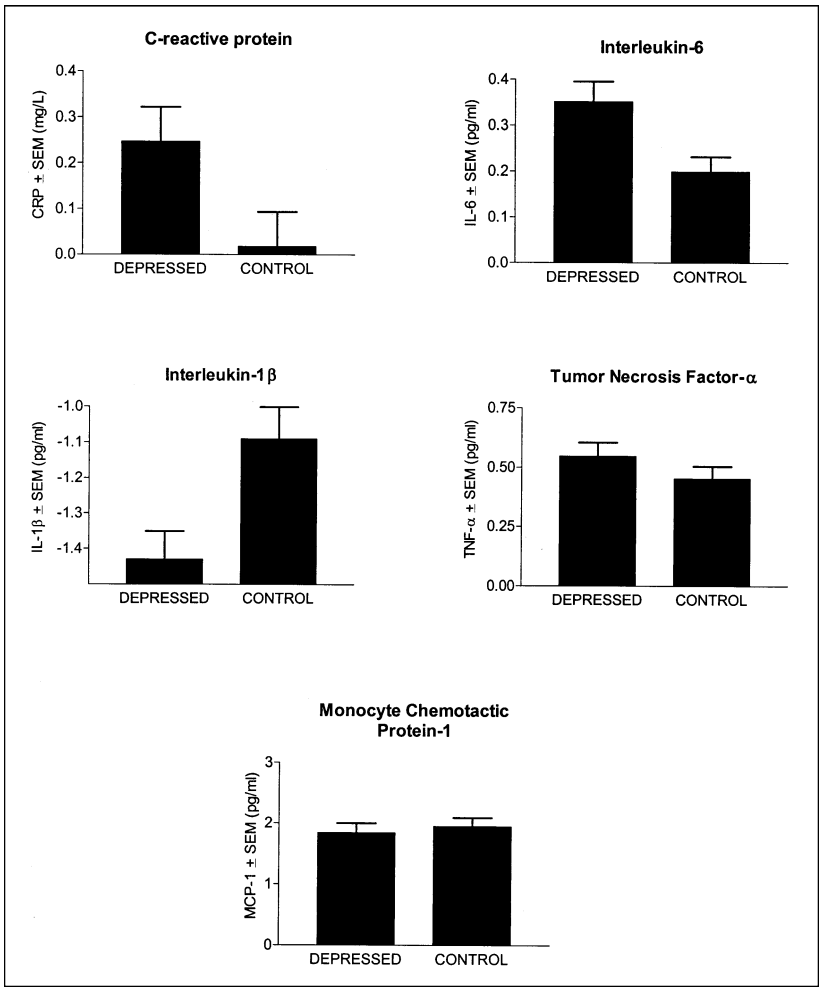

FIGURE 1. Circulating levels of inflammatory risk markers. Subjects with depression showed higher levels of CRP and interleukin-6 (IL-6), and lower levels of interleukin-1β (IL-1β) compared with control subjects ($p < 0.05$). There were no differences in tumor necrosis factor-α (TNF-α) or monocyte chemotactic protein-1 (MCP-1) ($p > 0.23$). Values are log-10 transformed.

DISCUSSION

The present study shows that in otherwise healthy adults, depression is accompanied by elevated levels of 2 inflammatory risk markers that have been implicated in CHD pathogenesis.[10,11,20] These elevations are fairly large; on average, subjects with depression exhibited 41% higher CRP levels and 54% higher interleukin-6 levels than control subjects. Although an association between depression and inflammation has been reported,[21–25] our study extends these findings by assessing patients with clinical depression, and showing that its effects are independent of demographic characteristics, chronic medical illness, acute infectious disease, gross nutritional status, use of prescription medication and illicit substances, and established cardiovascular risk factors.

We also sought to identify pathways through which depression may become associated with inflammation. Although subjects with depression reported higher rates of cigarette smoking than controls, this process did not contribute to their elevated levels of inflammatory markers. Increased susceptibility to infection with *Chlamydia pneumoniae* and cytomegalovirus also was not responsible; the rates of seropositivity to these pathogens were very similar between the groups. However, subjects with depression exhibited significantly greater adiposity than control subjects, and adjusting for body mass significantly attenuated the group differences in CRP and interleukin-6.

These findings suggest that whole-body adiposity is partially responsible for the elevated levels of CRP and interleukin-6 seen in subjects with depression. How might this process occur? Persons with clinical depression, perhaps by virtue of their sedentary behavior, may accumulate excess weight.[26] As this occurs, circulating levels of interleukin-6 would increase. Adipose tissue serves as a major source of this cytokine, accounting for nearly 30% of systemic interleukin-6.[27] With higher levels of circulating interleukin-6, hepatic synthesis of CRP would increase,[13] and leukocyte production of interleukin-1β would decline as a result of the negative feedback loop between these cytokines.[28] This cascade of events cannot completely explain the study's findings; however, we found evidence of a synergistic relation between depression and adiposity. What pathways might explain depression's relation with inflammation beyond its impact on adiposity? Dysregulation of hormonal systems is a likely candidate. Depression is often accompanied by activation of the sympathetic-adrenal-medullary and the hypothalamic-pituitary-adrenocortical axes.[7] The hormonal products of these axes, particularly epinephrine, can upregulate the expression of inflammatory molecules such as interleukin-6.[28] With prolonged exposure to cortisol, white blood cells may also downregulate their glucocorticoid receptors, rendering the immune system resistant to cortisol's anti-inflammatory properties.[7] This pattern of hormonal dysregulation may be especially pronounced in persons with depression with high levels of adiposity.

Because of the cross-sectional design of this study, it is not possible to specify the direction of causal relations between variables. For instance, it is possible that adiposity operates as the starting point in this process, triggering an inflammatory response that gives rise to depressive symptoms by way of neuroimmune pathways[29] and accelerates the progression of CHD simultaneously. A clear delineation of the

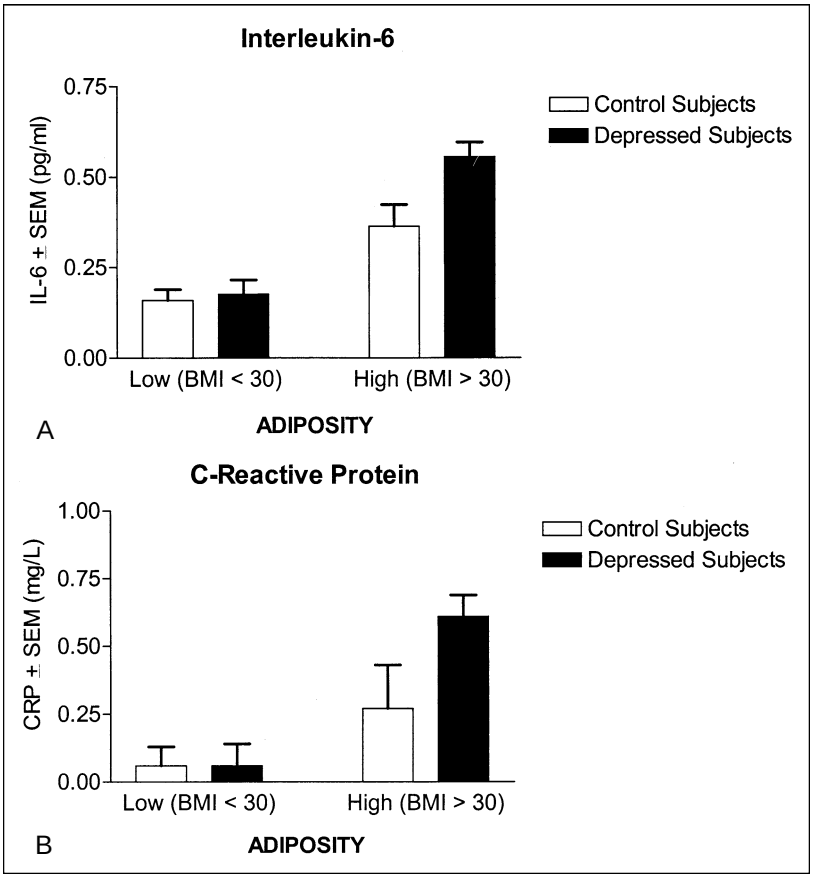

FIGURE 2. Synergistic relation between depression and adiposity. Subjects with depression with high body mass exhibited significantly higher levels of interleukin-6 *(A)* and CRP *(B)* compared with groups defined by other combinations of these factors (ps <0.001). Values are log-10 transformed. Abbreviation as in Figure 1.

relations among these processes will require prospective longitudinal investigations with more comprehensive assessments of each construct involved. Despite these limitations, the present study demonstrates that persons with clinical depression exhibit increased levels of the inflammatory risk markers CRP and interleukin-6. To the extent that an inflammatory response of this nature persists over time, it could foster a variety of pathogenic processes, including the development of insulin resistance, the growth of atherosclerotic plaque, the rupture or fissure of existing plaque, and the formation of occlusive thrombi.[8,9,28,30] This cascade of events could explain much of the excess morbidity and mortality seen in persons with depression in the metabolic and cardiovascular domains.

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