Special Article

SUICIDAL IDEATION IS ASSOCIATED WITH ELEVATED INFLAMMATION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

Aoife O'Donovan, Ph.D.,[1,2,3,4]* Gavin Rush, M.B.,[5] Gerard Hoatam, M.S.,[6] Brian M. Hughes, Ph.D.,[7] AnnMaria McCrohan, Ph.D.,[2] Cecily Kelleher, Ph.D.,[8] Cliona O'Farrelly, Ph.D.,[9] and Kevin M. Malone, M.D.[1,2]

Background: *Patients with major depressive disorder (MDD) who attempt or complete suicide have elevated inflammation compared to nonsuicidal patients with MDD. However, greater severity of depression and the medical lethality of suicide attempts could account for such elevated inflammation in suicide attempters and suicide completers.* **Methods:** *To clarify, we measured inflammatory markers in patients with MDD with and without high levels of suicidal ideation and in nondepressed controls (N = 124). Levels of suicidal ideation, depression severity, and recent suicide attempts were assessed by structured clinical interviews. A composite score including the inflammatory markers tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), and C-reactive protein (CRP) was used as an inflammatory index. Analysis of covariance models were used to assess group differences with adjustments for age and gender.* **Results:** *Patients with MDD and high suicidal ideation had significantly higher inflammatory index scores than both controls, $F(1,53) = 18.08$, partial $\eta^2 = .25$, $P < .001$, and patients with MDD and lower suicidal ideation $F(1,44) = 7.59$, partial $\eta^2 = .15$, $P = .009$. In contrast, patients with lower suicidal ideation were not significantly different from controls on the inflammatory index, $F(1,63) = .52$, partial $\eta^2 = .01$, $P = .47$. Follow-up analyses indicated that differences between patients with MDD and high versus lower suicidal ideation were independent of depression severity and recent suicide attempts.* **Conclusions:** *Suicidal ideation may be uniquely associated with inflammation in depressed patients. Depression and Anxiety 30:307–314, 2013.*

Key words: *depression; biological markers; mood disorders; stress; suicide/self-harm*

INTRODUCTION

The immune system is a new and important frontier in the quest to better understand and treat psychiatric disorders. Accumulating evidence now implicates the immune system and specifically inflammation in the development of disorders ranging from autism to

[1]School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland
[2]Department of Psychiatry, Psychotherapy and Mental Health Research, St. Vincent's University Hospital, Dublin, Ireland
[3]Stress and Health Research Program, San Francisco Veteran's Affairs Medical Center, San Francisco, California
[4]Department of Psychiatry, University of California, San Francisco, California
[5]St. Patrick's University Hospital, Dublin, Ireland
[6]School of Medicine, Creighton University, Omaha, Nebraska
[7]Department of Psychology, National University of Ireland, Galway, Ireland
[8]School of Public Health, Physiotherapy & Population Science, University College Dublin, Dublin, Ireland
[9]School of Biochemistry and Immunology, Trinity College, Dublin, Ireland

*Correspondence to: Aoife O'Donovan, Department of Psychiatry, University of California, San Francisco 3333 California Street, Suite 465, San Francisco, CA 94143-0848. E-mail: aoife.odonovan@ucsf.edu

Received for publication 2 October 2012; Revised 4 February 2013; Accepted 8 February 2013

DOI 10.1002/da.22087
Published online 15 March 2013 in Wiley Online Library (wileyonlinelibrary.com).

schizophrenia to depression.[1–3] Particularly strong evidence implicates inflammation in the development of depressive symptoms and major depressive disorder (MDD).[4–6] However, there is wide variability in the levels of inflammation observed in depressed individuals, and some studies have failed to find an association between depression and inflammation.[7–9] Research clarifying the relationship between specific depressive symptoms and inflammation is therefore necessary.

The relationship between depression and inflammation is complex and likely bidirectional. Animal studies have shown that inflammation promotes a pattern of behavior known as sickness behavior that includes symptoms of depression, such as fatigue, anhedonia, and social withdrawal.[10,11] Humans who are treated for cancer and hepatitis C with high doses of pro-inflammatory cytokines also demonstrate these symptoms and are at high risk for developing MDD.[12,13] However, one prospective study of patients receiving the pro-inflammatory cytokine interferon-α (IFN-α) for hepatitis C indicates that depression may also promote inflammation.[14] Moreover, in another large-scale prospective study of healthy adults, depressive symptoms predicted levels of inflammation 6 years later whereas inflammation did not likewise predict depressive symptoms.[15] Additionally, inflammatory responses to acute stress in the laboratory are exaggerated in depressed individuals, indicating that depression may also increase inflammation by promoting greater inflammatory responses to everyday stress.[16,17] Despite these apparently causal bidirectional relationships, however, depressed individuals have not demonstrated elevated inflammation in all studies,[7,8] and inflammation may be elevated in only a subset of depressed patients.[9]

Accumulating evidence suggests that levels of inflammation might be particularly high in suicidal depressed patients. First, inflammation may promote suicidal ideation. As evidence, increased suicidal ideation was observed in patients receiving pro-inflammatory cytokines compared with other treatments for hepatitis C,[18] and in patients receiving pro-inflammatory cytokines for the treatment of multiple sclerosis.[19] Second, suicidal ideation may promote inflammation. Suicidal depression is characterized by hopelessness and negative expectations for the future, which have previously been associated with elevated inflammation.[20,21] Additionally, the perception of threat that leads suicidal individuals to contemplate suicide may activate biological stress responses, including inflammatory responses.[22–24] Thus, patients with suicidal depression may have higher levels of inflammation than nonsuicidal depressed patients.

In line with this hypothesis, a small body of literature now documents associations between suicidal behavior and inflammation. Higher levels of messenger RNA for the inflammatory markers interleukin-4 (IL-4) and interleukin-13 (IL-13) was found in the orbitofrontal cortex of individuals who died by suicide compared with individuals who died from other causes.[25] However, both increased[25–27] and decreased[28] levels of circulating peripheral inflammatory markers have been observed in suicide attempters compared with nonattempters. A complication in the interpretation of these studies is that suicide attempts may be associated with high levels of physical trauma, which could in itself have strong influences on systemic inflammatory markers. In fact, patients who made a violent suicide attempt showed the highest levels of the pro-inflammatory cytokine interleukin-6 (IL-6) in one study.[27] Studies linking suicidal ideation with inflammation are not similarly confounded. However, little is known about the relationship between suicidal ideation and inflammation in individuals without comorbid physical diseases.

The aim of the present study was to investigate differences in inflammatory markers between patients with MDD and high versus lower levels of suicidal ideation, and further to compare inflammation in these two groups with that of nondepressed healthy controls. We measured levels of the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and IL-6, the anti-inflammatory cytokine interleukin-10 (IL-10), the regulatory cytokine transforming growth factor-beta (TGF-β), and the acute phase protein C-reactive protein (CRP) in hospital in-patients with MDD and healthy controls. It is well-established that the hypothalamic–pituitary–adrenal (HPA) axis exerts important regulatory influences on inflammation[29] and numerous studies have documented HPA axis abnormalities in MDD.[30] To examine if altered HPA axis activity accounted for any observed group differences in inflammatory markers, we measured circulating levels of adrenocorticotropic hormone (ACTH) and cortisol. We hypothesized that patients with MDD would have higher levels of inflammation, ACTH, and cortisol than healthy controls and that among patients with MDD, those with high suicidal ideation would have the highest levels of inflammation, ACTH, and cortisol. We also hypothesized that these group differences between patients with and without high suicidal ideation would be independent of depression severity and recent suicide attempts.

METHODS

PARTICIPANTS

Our sample included 76 hospital in-patients with a primary diagnosis of MDD and 48 healthy controls. Hospital in-patients with MDD were recruited from two large urban hospitals in Dublin, Ireland. Comparison participants without MDD were recruited via flyers and e-mails circulated in the community. Exclusion criteria included lack of a primary diagnosis of MDD for the patient group, and the presence of acute physical illnesses and age below 18 years for all participants. The institutional ethics committees at each of the hospitals where data were collected approved the study, and all participants provided written informed consent.

PROCEDURES

Fasting blood samples for the measurement of inflammatory markers, ACTH, and cortisol were collected between 07:00 h and 09:00 h.

Trained and calibrated clinical interviewers administered structured clinical interviews within 24 hr of the blood draw, and participants completed self-report questionnaires within 1 week.

MEASURES

Psychiatric Diagnosis. The Mini International Neuropsychiatric Instrument 5.0.0 (MINI) is a structured interview for the assessment of psychiatric symptoms and disorders based on the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV-TR), which has high diagnostic concordance with the Structured Clinical Interview for DSM-IV.[31] Two trained and calibrated interviewers conducted all structured interviews for the present study.

Depression Severity. Severity of depression was assessed with the Hamilton Rating Scale for Depression (HAM-D).[32] The HAM-D is a structured interview measure, which assesses the severity of 17 depressive symptoms during the past week. The same trained and calibrated interviewers who conducted the MINI administered the HAM-D. The scale had acceptable reliability in our sample (Cronbach's $\alpha = .91$).

Suicidal Ideation. Suicidal ideation was assessed with the MINI, which includes six questions relating to suicidal thoughts and plans, and suicide attempts.[31] Scores on the MINI suicidal ideation scale range from 0 to 33 with scores from 0 to 5 indexing low risk, 6–9 indexing moderate risk, and $\geq$10 indexing high risk for suicide. Patients were classified as having high suicidal ideation if they had a score $\geq$10, which equates to active ideation with a recent suicide plan or attempt, and as lower suicidal ideation if they had a score below 10. Suicidal ideation data were missing for two patients and these patients were therefore excluded from analyses of suicidal ideation. The scale had acceptable reliability in our sample (Cronbach's $\alpha = .88$).

Demographic and Clinical Information. Demographic and clinical information was collected through self-report and was validated by medical chart review when necessary and possible. Patients reported their number of prior episodes of depression, estimated duration of MDD, and duration of antidepressant treatment during a structured interview.

Body Mass Index (BMI). Weight and height were measured by trained research assistants, and BMI was calculated as weight in kilograms divided by height in meters squared. BMI data were missing for 29 patients with MDD.

Anti-Inflammatory Medication. Use of anti-inflammatory medications including nonsteroidal anti-inflammatory medications and statins was assessed by self-report, validated by chart review where possible.

Inflammation. Samples were collected in 5 ml EDTA coated tubes (BD Vacutainer, Franklin Lakes, NJ). High-sensitivity enzyme-linked immunosorbent assays (ELISAs) were used to quantify plasma levels of IL-6, TNF-α, IL-10 (R&D Systems, Minneapolis, MN) and TGF-β (Invitrogen Corporation, Carlsbad, CA). High-sensitivity CRP analyses were conducted by means of a particle-enhanced immunonephelometry assay using *CardioPhase* hsCRP reagents on the BN System (Dade Behring, Deerfield, IL). The lower limits of detection for these assays were as follows: 0.07 pg/ml for IL-6; 0.5 pg/ml for IL-10; 0.11 for TNF-α; 15.6 pg/ml for TGF-β; and 0.16 mg/l for hsCRP. All samples were assayed in duplicate and the coefficients of variation for these assays were <12%. Due to limited availability of biological samples, we had incomplete data and missing TNF-α for 6 MDD patients and 1 control; IL-6 for 5 MDD patients and 1 control; IL-10 for 3 MDD patients; TGF-β for 13 MDD patients and 3 controls; and CRP for 22 MDD patients and 10 controls.

HPA Axis Activity. Samples were collected in 5 ml serum separator tubes (BD Vacutainer, Franklin Lakes, NJ). Serum levels of ACTH and cortisol were measured by immunoassay using the Immulite 2500 from Siemens Diagnostics, Tarrytown, NY. ACTH was available for 14 controls and 44 patients, and cortisol was available for 43 controls and 55 patients. The mean inter- and intra-assay coefficients of variation were <9% for ACTH for cortisol.

DATA ANALYSIS

Patients with MDD and a MINI Suicidal Ideation score greater than 10 were defined as high suicidal ideation and those with MDD and a score below 10 were defined as lower suicidal ideation. Principal components analysis was used to identify variables for inclusion in an inflammatory index score and the cutoff for inclusion of variables within this factor was set at .40. A series of analysis of covariance (ANCOVA) models were used to compare levels of inflammatory markers, ACTH, and cortisol between patients with MDD and controls, controlling for age and gender. ANCOVA models were used again to examine differences in levels of inflammatory markers, ACTH, and cortisol among controls and patients with MDD and high or lower suicidal ideation, controlling for age and gender in the first instance, and additionally controlling for depression severity and suicide attempts in follow-up analyses including only patients with MDD. Linear regression models were used to contrast the amount of variance in inflammation associated with depression severity and suicidal ideation group status. Student's *t*-tests were used to examine group differences in continuous variables and crosstabs were used to assess group differences in categorical variables. Negative reciprocal transformations were used to improve the distributions of inflammatory markers, ACTH, and cortisol. SPSS 18 was used for all statistical analysis (SPSS, Inc.) and the significance level was set at $P < .05$.

INFLAMMATORY INDEX

Principal components analysis revealed that TNF-α, IL-6, IL-10, and CRP had loadings greater than .40 on a single factor (range: .49–.69), but that the loading for TGF-β was less than .40 at −.29. Based on these factor loadings, we created a summary inflammatory index score by calculating the sum of *z* scores for IL-6, TNF-α, IL-10, and CRP. Only participants who had data available on all four of these markers were included in these analyses and, thus, the sample size for analyses using the inflammatory index was 86. Analyses on the individual inflammatory markers include all available data.

RESULTS

SAMPLE CHARACTERISTICS

Table 1 includes information on controls and patients with MDD and high or lower levels of suicidal ideation. Among the three groups, there were significant differences in age ($F(2,119) = 3.93$, $P = .02$), but not gender ($\chi^2 = .72$, $P = .70$), BMI ($F(2,92) = .85$, $P = .43$), or use of anti-inflammatory medications ($\chi^2 = 1.92$, $P = .38$). Among participants with MDD, those with high levels of suicidal ideation were significantly older than those with lower levels of suicidal ideation ($t = 2.04$, $P = .04$), but there were no group differences in gender ($\chi^2 = .71$, $P = .40$), BMI ($t = .76$, $P = .45$), number of episodes of depression experienced ($t = .73$, $P = .47$), estimated duration of MDD in years ($t = .35$, $P = .73$), duration of antidepressant treatment ($t = .56$, $P = .58$), or use of anti-inflammatory medications ($\chi^2 = .89$, $P = .34$).

All of the inflammatory markers were positively associated with one another (*r* range: .31–.02, *P* range: .001–.89), with the exception of TGF-β, which was negatively associated with the other inflammatory markers

TABLE 1. Sample characteristics of control participants and participants with major depression and high or lower levels of suicidal ideation

	Controls $N = 48$	Lower suicidal ideation $N = 45$	High suicidal ideation $N = 29$	P^*	P^{**}
Age	45.85 (2.23)	54.09 (2.39)	47.00 (2.18)	.06	.04
Gender	14M/34F	15M/30F	7M/22F	.90	.71
BMI	25.05 (0.62)	27.34 (6.93)	25.42 (1.83)	.39	.45
HAMD	3.13 (1.20)	27.20 (1.36)	33.05 (1.77)	<.001	.01
ACTH (pg/ml)	24.17 (3.71)	26.95 (2.54)	25.05 (3.13)	.16	.66
Cortisol (nmol/l)	467.85 (24.97)	517.60 (27.49)	534.05 (34.55)	.26	.67
TNF-α (pg/ml)	2.69 (0.42)	3.54 (0.58)	3.82 (0.71)	.31	.97
IL-6 (pg/ml)	0.77 (0.41)	1.72 (0.55)	2.58 (0.68)	.002	.02
IL-10 (pg/ml)	4.00 (4.85)	4.41 (6.39)	20.41 (7.97)	.05	.06
CRP (mg/l)	1.68 (0.68)	2.94 (0.90)	4.46 (1.13)	.08	.02
TGF-β (pg/ml)	14849.22 (3422.98)	18754.21 (4485.68)	14123.26 (5705.32)	.15	.42

The P^* column includes P values for differences between controls and patients with MDD, and the P^{**} column includes P values for differences between patients with MDD and high versus lower levels of suicidal ideation. Means are based on raw data and P values based on reciprocal transformed data.

ACTH, adrenocorticotropic hormone; BMI, body mass index; CRP, C-reactive protein; F, female; HAMD, Hamilton Depression Rating Scale score; IL-6, intereleukin-6; IL-10, interleukin-10; M, male; MDD, major depressive disorder; *N*, number of participants; *SE*, standard error of mean; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

(r range: $-.21$ to $-.05$, P range: .03–.59). Cortisol and ACTH were significantly and positively associated with one another ($r = .61$, $P < .001$), but neither of these was significantly associated with any of the inflammatory markers. Older individuals had significantly higher scores on the inflammatory index ($r = .37$, $P = .001$), and there was a trend toward lower scores on the inflammatory index in women ($t = 1.65$, $P = .10$).

MDD AND INFLAMMATION

Patients with MDD had significantly higher levels of inflammation, as indexed by the inflammatory index ($F(1,82) = 5.63$, partial $\eta^2 = .06$, $P = .02$. Follow-up analyses indicated that patients with MDD had significantly higher levels of IL-6, $F(1,114) = 10.08$, partial $\eta^2 = .08$, $P = .002$, and IL-10, $F(1,117) = 3.87$, partial $\eta^2 = .03$, $P = .05$, than control participants (see Fig. 1). There was also a trend toward higher levels of CRP in patients with MDD but this was not statistically significant, $F(1,88) = 3.21$, partial $\eta^2 = .03$, $P = .08$, and patients with MDD were not significantly different from controls on the other biological variables.

SUICIDAL IDEATION AND INFLAMMATION

Our next set of analyses compared levels of biological markers among controls and patients with high and lower levels of suicidal ideation. Analyses based on the inflammatory index indicated significant differences in inflammation among the three groups, $F(2,81) = 7.10$, partial $\eta^2 = .15$, $P = .001$. Patients with high suicidal ideation had significantly higher inflammatory index scores than both controls, $F(1,53) = 18.08$, partial $\eta^2 = .25$, $P < .001$, and patients with MDD and lower levels of suicidal ideation, $F(1,44) = 7.59$, partial $\eta^2 = .15$, $P = .009$. However, patients with lower suicidal ideation were not significantly different from controls on the inflammatory index, $F(1,63) = .52$, partial $\eta^2 = .01$, $P = .47$.

Follow-up analyses on the individual inflammatory markers indicated that patients with high suicidal ideation had significantly higher levels of IL-6, $F(1,71) = 15.97$, partial $\eta^2 = .18$, $P < .001$, and CRP, $F(1,55) = 6.46$, partial $\eta^2 = .10$, $P = .01$, and a trend toward lower levels of IL-10, $F(1,72) = 2.98$, partial $\eta^2 = .04$, $P = .09$, than controls, whereas lower suicidal ideation patients were not significantly different from controls on any of the individual inflammatory markers (Ps > .15).

Patients with MDD and high suicidal ideation also had significantly higher levels of IL-6, $F(1, 66) = 5.45$, partial $\eta^2 = 0.08$, $P = .02$, and CRP, $F(1,50) = 5.46$, partial $\eta^2 = .10$, $P = .02$, than patients with MDD and lower suicidal ideation. These high suicidal ideation patients also exhibited a nonsignificant trend toward higher levels of IL-10, $F(1, 67) = 3.62$, $\eta^2 = 0.05$, $P = .06$, than patients with lower levels of suicidal ideation, but there were no differences between these groups on ACTH, cortisol, or other markers of inflammation. Separate analyses were conducted with TGF-β as an outcome. Results indicated no significant group differences in TGF-β in any of the contrasts. Figure 1 shows significant group differences in the inflammatory index and individual inflammatory markers.

DEPRESSION SEVERITY AND RECENT SUICIDE ATTEMPTS

Importantly, patients with high suicidal ideation reported higher severity of depressive symptoms than those with low suicidal ideation ($t = 2.64$, $P = .01$), even when the HAM-D item that assesses suicidal ideation

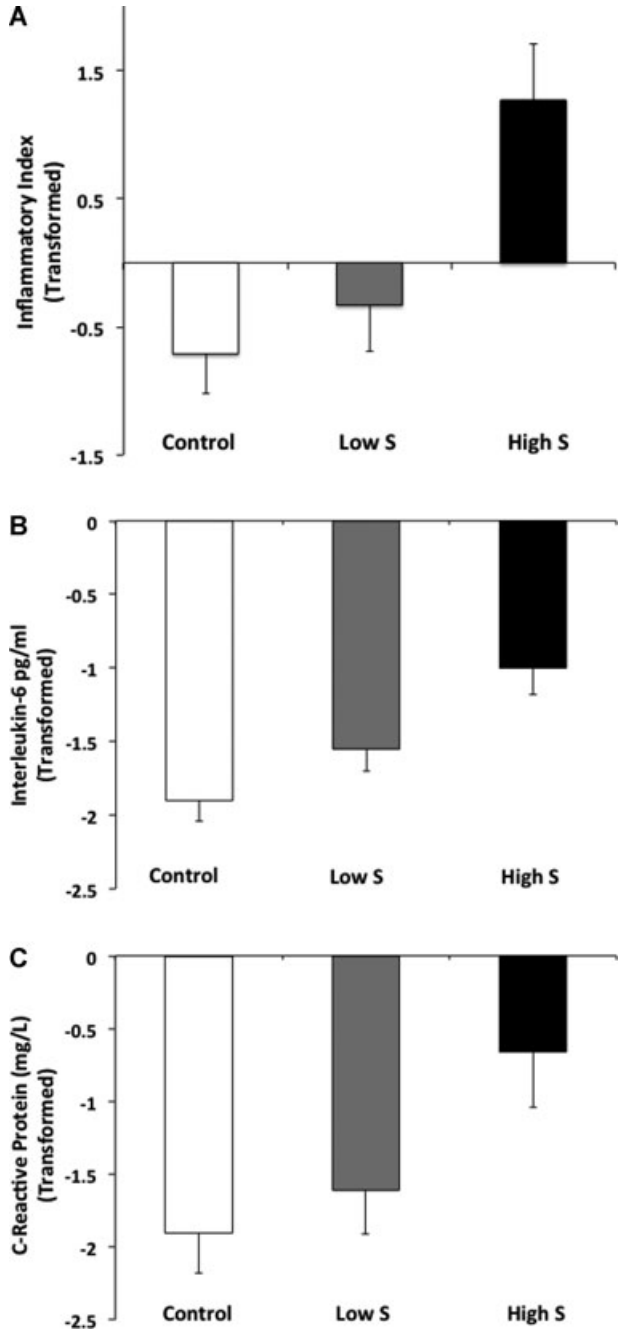

Figure 1. Figures show levels of the inflammatory index (A) and the individual inflammatory markers interleukin-6 (IL-6) (B), and C-reactive protein (CRP) (C) in controls, patients with major depressive disorder (MDD) and lower suicidal ideation, and patients with MDD and high suicidal ideation. Patients with MDD and high suicidal ideation had significantly higher levels of IL-6 and CRP than patients with lower suicidal ideation and control participants. These figures include estimated marginal means and standard errors of negative reciprocally transformed data, which was adjusted for age and gender in order to illustrate group differences after covarying for these factors.

was omitted ($t = 1.98$, $P = .05$), underlining the possibility that severity of depression could account for the observed association between suicidal ideation and inflammation. Thus, we reran the analysis adding HAM-D scores without the suicidal ideation item as a covariate. In these analyses, high suicidal ideation patients continued to demonstrate significantly higher levels of inflammation as indexed by the inflammatory index, $F(1,43) = 6.13$, partial $\eta^2 = .12$, $P = .02$, and higher levels of IL-6, $F(1, 65) = 4.28$, partial $\eta^2 = .06$, $P = .04$, and CRP, $F(1, 49) = 4.63$, partial $\eta^2 = 0.09$, $P = .04$, than patients with low suicidal ideation. In a linear multiple regression model, depression severity accounted for a nonsignificant 5% of variance in the inflammatory index, $F_{\text{Change}}(1,44) = 2.38$, $P = .13$, whereas suicidal ideation group status accounted for a significant 13% of variance, $F_{\text{Change}}(1,43) = 7.87$, $P = .008$.

Our sample included 12 patients who had attempted suicide in the previous month ($n = 6$ with inflammatory index scores) and we examined if a suicide attempt in the past month was associated with increased levels of inflammation by comparing levels of inflammation between patients who had attempted suicide in the past month and all other patients with MDD. Results indicated no significant differences between suicide attempters and nonattempters on any of the inflammatory markers, including the inflammatory index ($t = .42$, $P = .68$), IL-6 ($t = .40$, $P = .69$), and CRP ($t = .87$, $P = .38$). In addition, when we controlled for recent suicide attempts in our main analytic model, our pattern of results remained the same.

DISCUSSION

The present study provides evidence that suicidal ideation appears uniquely associated with elevated inflammation in hospital in-patients with MDD. In our sample, patients with MDD who had high levels of suicidal ideation showed significantly elevated levels of inflammation, particularly as indexed by IL-6 and CRP, when compared with patients whose levels of suicidal ideation were lower. Moreover, only those patients with high levels of suicidal ideation exhibited significantly higher levels of inflammation when compared with healthy controls. Finally, the data suggested that the relationship between suicidal ideation and inflammation was independent of possible confounds, such as depression severity and recent suicide attempts.

The present findings are in line with previous research showing that suicide attempters have higher levels of inflammatory markers than comparison participants without a history of suicide attempts.[26,27] They are also consistent with a previous report suggesting that levels of inflammatory markers are elevated in the brains of suicide completers.[25] The present data extend this previous research in suggesting that having high levels of suicidal ideation alone may be associated with elevated inflammation. It is difficult to draw any conclusions about specificity in the relationship between

suicidal ideation and inflammation from this body of work. We found that only two of the individual inflammatory markers were elevated in high suicidal ideation patients compared with patients with lower levels of suicidal ideation. These markers, IL-6 and CRP, are systemic markers of inflammation that are typically associated with higher levels of inflammation, but they can also have immunoregulatory and anti-inflammatory effects.[33,34] Meanwhile, the anti-inflammatory cytokine IL-10 was significantly elevated in patients with MDD overall compared with controls, and there was a trend toward higher levels of IL-10 in high suicidal ideation patients compared with controls. Thus, although speculative for now, this pattern of activation may represent an attempt to downregulate inflammation in suicidally depressed patients.

The relationship between suicidal ideation and inflammation may be bidirectional. Inflammation is increasingly recognized as playing a causal role in the development of at least some forms of depression,[3,35] and one plausible explanation for our findings is that suicidal ideation is more common in individuals with inflammation-associated depression. One previous report suggested that levels of kynurenine, which can be stimulated by inflammation, are elevated in patients with MDD with versus without a history of a suicide attempt.[36] Kynurenine, in turn, is thought to play a key role in inflammation-associated depression.[3] Thus, taken together, the evidence indicates that patients with inflammation-associated depression, whether due to a comorbid physical illness or treatment with pro-inflammatory proteins, are at high risk for suicidal ideation.

Another potential explanation is that suicidal ideation in and of itself promotes inflammation in depressed patients. In particular, hopelessness and perceived psychological stress may promote inflammation in suicidal individuals.[22,23,37] Although the relationship between suicidal ideation and inflammation was independent of depression severity in our sample, patients with high suicidal ideation did have more severe depressive symptoms. Thus, suicidal ideation may promote inflammation in patients with MDD, and inflammation in turn may exacerbate depressive symptoms.

The biological mechanisms linking suicidal ideation with inflammation also remain to be elucidated. Acute threat exposure is associated with increased HPA axis activity as indexed by higher levels of cortisol,[23] and cortisol in turn generally has anti-inflammatory effects.[29] Thus, a dysregulated HPA axis could play a role in the relationship between suicidal ideation and inflammation. In the small number of participants for whom we measured ACTH and cortisol, we found no evidence for differences between groups and, thus, no support for the hypothesis that HPA axis dysregulation contributed to the observed group differences in inflammation. However, circulating basal levels of ACTH and cortisol do not provide complete information on activity of the HPA axis, which functions through feedback loops involving the expression of proteins as well as receptors. Moreover, although ACTH and cortisol were measured in blood samples collected during the morning hours in all participants (07:00–09:00 h), this restriction may have been insufficient to control for strong circadian variation in these hormones. Future studies should measure these markers on multiple occasions during the circadian cycle.

LIMITATIONS

The present results must be considered in the context of several limitations. First, the cross-sectional study design and small sample size limits causal conclusions regarding the relationship between suicidal ideation and inflammation. Second, patients in our study were hospital in-patients taking antidepressant and other psychotropic medications and some participants were using anti-inflammatory medications, all of which could have influenced levels of our dependent variables.[38] Although our results appeared independent of duration of antidepressant treatment and presence versus absence of anti-inflammatory treatments, it was not possible to adequately adjust for pharmacological effects on our results. Third, the observed group difference in inflammation between patients with high versus lower levels of inflammation appeared independent of depression severity in our sample. However, we used a structured interview measure of depression severity (HAM-D) and results may have been different if we had employed a self-report measure. Fourth, our sample included only a small number of patients who had made a suicide attempt in the previous month ($n = 12$ total and $n = 6$ with data on all inflammatory markers). Thus, our finding that there was no significant differences in inflammatory markers between suicide attempters and nonattempters must be interpreted with caution. Finally, our study cannot account for lifetime stress exposure or comorbid psychiatric disorders that could have contributed to our observed pattern of results.

CLINICAL AND PUBLIC HEALTH RELEVANCE

The World Health Organization ranks suicide as one of the leading causes of death worldwide, accounting for 1.4% of all deaths.[39] For every completed suicide, there are as many as 60 suicide attempts that do not result in death[40] and suicidal ideation is even more prevalent with a lifetime prevalence of 13%.[41] Completed suicide, attempted suicide, and suicidal ideation are much more common in patients with MDD with one study estimating that 40% of people attempt suicide within 5 years after the first episode of MDD,[42] and more than half of those who make a suicide plan have MDD.[43] Thus, the present results are relevant to a large minority of patients with MDD. The findings suggest that further research on inflammation as a contributor to the pathophysiology of suicidal depression is warranted and could even yield novel adjunct treatments for MDD. Finally, the data suggest that suicidal depressed patients may be

at increased risk for inflammatory disorders including chronic diseases of aging and may benefit from treatments targeting inflammation and psychological stress. However, caution is required because emerging evidence indicates that some anti-inflammatory treatments may antagonize the effects of commonly used antidepressant treatments including selective serotonin reuptake inhibitors.[44]

CONCLUSIONS

The present data suggest that suicidal ideation is uniquely associated with elevated inflammation, controlling for depression severity and recent suicide attempts. In fact, in our sample of hospital in-patients with MDD, only those with high suicidal ideation exhibited elevations in inflammatory markers compared with healthy controls. In sum, our data indicate that suicidal ideation and inflammation appear uniquely interlinked in patients with depression.

Acknowledgments. This study was supported by the Craig Dobbin Newman Scholarship in Mental Health Research and Society in Science – The Branco Weiss Fellowship to A.O.D. and by a Lundbeck Research Scholarship to G.R. The authors would like to thank Josh Woolley, M.D./Ph.D., Ashkan Ahmadian, B.A., and Kristen Nishimi, B.A., for helpful feedback on this manuscript.

REFERENCES

1. Onore C, Careaga M, Ashwood P. The role of immune dysfunction in the pathophysiology of autism. Brain Behav Immun 2012;26:383–392.
2. Potvin S, Stip E, Sepehry AA, et al. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry 2008;63:801–808.
3. Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46–56.
4. Maes M, Meltzer HY, Bosmans E, et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J Affect Disord 1995;34:301–309.
5. Alesci S, Martinez PE, Kelkar S, et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. J Clin Endocrinol Metab 2005;90:2522–2530.
6. Hestad KA, Tonseth S, Stoen CD, et al. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. J ECT 2003;19:183–188.
7. O'Donovan A, Hughes BM, Slavich GM, et al. Clinical anxiety, cortisol and interleukin-6: evidence for specificity in emotion-biology relationships. Brain Behav Immun 2010;24:1074–1077.
8. Whooley MA, Caska CM, Hendrickson BE, et al. Depression and inflammation in patients with coronary heart disease: findings from the Heart and Soul Study. Biol Psychiatry 2007;62:314–320.
9. Glassman AH, Miller GE. Where there is depression, there is inflammation . . . sometimes! Biol Psychiatry 2007;62:280–281.
10. O'Connor JC, Lawson MA, Andre C, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol Psychiatry 2009;14:511–522.
11. Goshen I, Kreisel T, Ben-Menachem-Zidon O, et al. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. Mol Psychiatry 2008;13:717–728.
12. Capuron L, Ravaud A, Gualde N, et al. Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. Psychoneuroendocrinology 2001;26:797–808.
13. Capuron L, Gumnick JF, Musselman DL, et al. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 2002;26:643–652.
14. Prather AA, Rabinovitz M, Pollock BG, et al. Cytokine-induced depression during IFN-alpha treatment: the role of IL-6 and sleep quality. Brain Behav Immun 2009;23:1109–1116.
15. Stewart JC, Rand KL, Muldoon MF, et al. A prospective evaluation of the directionality of the depression-inflammation relationship. Brain Behav Immun 2009;23:936–944.
16. Miller GE, Rohleder N, Stetler C, et al. Clinical depression and regulation of the inflammatory response during acute stress. Psychosom Med 2005;67:679–687.
17. Pace TW, Mletzko TC, Alagbe O, et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry 2006;163:1630–1633.
18. Dieperink E, Ho SB, Tetrick L, et al. Suicidal ideation during interferon-alpha2b and ribavirin treatment of patients with chronic hepatitis C. Gen Hosp Psychiatry 2004;26:237–240.
19. Fragoso YD, Frota ER, Lopes JS, et al. Severe depression, suicide attempts, and ideation during the use of interferon beta by patients with multiple sclerosis. Clin Neuropharmacol 2010;33:312–316.
20. MacLeod AK, Tata P, Tyrer P, et al. Hopelessness and positive and negative future thinking in parasuicide. Br J Clin Psychol 2005;44:495–504.
21. O'Donovan A, Lin J, Dhabhar FS, et al. Pessimism correlates with leukocyte telomere shortness and elevated interleukin-6 in postmenopausal women. Brain Behav Immun 2009;23:446–449.
22. Dickerson SS, Gable SL, Irwin MR, et al. Social-evaluative threat and proinflammatory cytokine regulation: an experimental laboratory investigation. Psychol Sci 2009;20:1237–1244.
23. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psych Bull 2004;130:355–391.
24. Melamed S, Shirom A, Toker S, et al. Association of fear of terror with low-grade inflammation among apparently healthy employed adults. Psychosom Med 2004;66:484–491.
25. Tonelli LH, Stiller J, Rujescu D, et al. Elevated cytokine expression in the orbitofrontal cortex of victims of suicide. Acta Psychiatr Scand 2008;117:198–206.
26. Janelidze S, Mattei D, Westrin A, et al. Cytokine levels in the blood may distinguish suicide attempters from depressed patients. Brain Behav Immun 2011;25:335–339.
27. Lindqvist D, Janelidze S, Hagell P, et al. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. Biol Psychiatry 2009;66:287–292.
28. Kim YK, Lee SW, Kim SH, et al. Differences in cytokines between non-suicidal patients and suicidal patients in major depression. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:356–361.

29. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995;332: 1351–1363.
30. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends Neurosci 2008;31:464–468.
31. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl 20):22–33.
32. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
33. Tilg H, Dinarello CA, Mier JW. IL-6 and APPs: anti-inflammatory and immunosuppressive mediators. Immunol Today 1997;18:428–432.
34. Yasukawa H, Ohishi M, Mori H, et al. IL-6 induces an anti-inflammatory response in the absence of SOCS3 in macrophages. Nat Immunol 2003;4:551–556.
35. Maes M. Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. Prog Neuropsychopharmacol Biol Psychiatry 2011;35: 664–675.
36. Sublette ME, Galfalvy HC, Fuchs D, et al. Plasma kynurenine levels are elevated in suicide attempters with major depressive disorder. Brain Behav Immun 2011;25:1272–1278.
37. Blascovich J, Mendes WB. Social psychophysiology and embodiment. In: Fiske ST, Gilbert DT, editors. The Handbook of Social Psychology. 5th ed. New York: Wiley; 2010;194–227.
38. Hiles SA, Baker AL, de Malmanche T, et al. Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis. Psychol Medicine 2012;1:1–12.
39. World Health Organization Revised Global Burden of Disease (GBD); 2004. Available at: http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html
40. Centers for Disease Control and Prevention, National Centers for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS); 2005 [cited 2012 September 19]; Available at: http://www.cdc.gov/injury/wisqars/index.html.
41. Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. Arch Gen Psychiatry 1999;56:617–626.
42. Malone KM, Haas GL, Sweeney JA, et al. Major depression and the risk of attempted suicide. J Affect Disord 1995;34:173–185.
43. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey replication. Arch Gen Psychiatry 2005;62:593–602.
44. Warner-Schmidt JL, Vanover KE, Chen EY, et al. Antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) are attenuated by anti-inflammatory drugs in mice and humans. Proc Natl Acad Sci USA 2011;108:9262–9267.