Inflammatory Markers in Acute Myocardial Infarction Patients: Preliminary Evidence of a Prospective Association With Depressive Symptoms

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Inflammatory activity has been associated with both coronary disease and depressive symptoms. We sought to determine whether inflammatory markers in myocardial infarction (MI) patients are prospectively associated with depressive symptomatology. Participants were a convenience sample of MI patients. Depressive symptoms were assessed soon after the MI and again 7 months postdischarge. Inflammatory markers examined were interleukin-6 (IL-6) and interleukin-1β. Results suggest no significant cross-sectional association between inflammatory markers and depressive symptoms at baseline. However, bivariate and multiple regression analyses revealed a significant positive prospective association between baseline IL-6 and depressive symptoms 7 months later ($\beta = .57$, $p < .01$). The results suggest that temporal considerations are important in understanding relationships between inflammation and depressive symptoms following MI.

Inflammatory activity has been implicated in the development and progression of atherosclerosis as well as in the precipitation of myocardial infarction (MI) through destabilization, erosion, and rupture of the atherosclerotic plaque (Ross, 1999; Whicher, Biasucci, & Rifal, 1999). Indeed, it has been hypothesized

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Journal of Applied Biobehavioral Research, 2007, **12,** 2, pp. 65–81.

that inflammation is the primary pathological process driving plaque development following initial endothelial damage (Whicher et al.). Inflammatory markers, such as interleukin-6 (IL-6), have been associated with the increased risk for acute coronary events both in healthy individuals and in patients with coronary heart disease (CHD; Ridker, Rifai, Stampfer, & Hennekens, 2000; Whicher et al.).

Inflammatory processes are also related to certain psychological variables, including depression, which itself has been implicated as a potential risk factor for CHD (Kop, 2003). The relationship between depression and the immune system has received considerable attention (e.g., Anisman & Merali, 2002; Capuron & Dantzer, 2003; Kronfol & Remick, 2000), stimulated in part by human and animal studies showing bidirectional interactions between inflammatory processes and the central nervous system (Maier & Watkins, 2000). Inflammatory activity, particularly that involving proinflammatory cytokines such as interleukin-1β (IL-1β) and IL-6, has been implicated in the production of a depressive "sickness behavior" syndrome that includes feelings of weakness, malaise, listlessness, inability to concentrate, lethargy, and apathy (Dantzer, 2002). At the same time, depression appears to be associated with alterations in the production of proinflammatory cytokines (i.e., tumor necrosis factor-α [TNF-α], IL-1β, and IL-6; Kiecolt-Glaser, Robels, & Glaser, 2002). To date, most research on depression and inflammatory activity has been conducted in healthy populations. The findings generally suggest a positive association between inflammatory activity and concurrent depressive symptoms (e.g., Dentino et al., 1999; Maes et al., 1995), although exceptions have been reported (Steptoe, Kunz-Ebrecht, & Owen, 2003).

We are aware of seven cross-sectional studies that have examined inflammation in relation to depressive symptoms in cardiac patients. Appels, Bar, Bar, Bruggeman, and de Bates (2000) found that among male CHD patients about to undergo angioplasty, IL-1β and TNF-α were associated cross-sectionally with vital exhaustion, a condition involving fatigue and hopelessness, and found that IL-6 showed a trend toward the same association. This relationship remained in evidence even on the exclusion of data for three patients with major depression (who showed elevated values for inflammatory markers).

A study conducted by Janszky, Lekander, Blom, Georgiades, and Ahnve (2005) examined inflammatory activity (i.e., IL-1β, IL-6, and c-reactive protein [CRP]) in a group of women 1.5 years post-MI. Results from this study suggest a positive association between IL-6 and both vital exhaustion and self-rated health. CRP showed a borderline significant association with the same measures. Inflammatory markers were not related to overall depression cross-sectionally.

In another cross-sectional study, Lesperance, Frasure-Smith, Theroux, and Irwin (2004) examined patients with a recent MI. Plasma concentrations of the

intercellular adhesion molecule-1, a surface glycoprotein that promotes cell adhesion and a possible indicator of inflammatory activity, were positively associated with a diagnosis of major depression. By contrast, IL-6 was unrelated to depression. For CRP, there was a significant interaction between depression and statin therapy, such that depression was positively associated with CRP only for those patients not taking statins.

Miller and colleagues examined the association between inflammatory activity and depression in a sample of patients who experienced acute coronary syndromes within the past 3 months, including MI, bypass surgery, and coronary angioplasty patients. Results suggested a positive association between CRP and depression (Miller, Freedland, Duntley, & Carney, 2005). A subsequent report on a subset of the same patients presented evidence of an association between depression and an in vitro measure of sensitivity to anti-inflammatory properties of glucocorticoids, but no relationship between depression and an in vitro measure of the inflammatory response to infection (Miller, Freedland, & Carney, 2005).

Annique et al. (2005) examined the relationship between depression and inflammatory activity in patients enrolled in a multisite investigation of depression and MI. Patients were divided into depressed and nondepressed groups that were matched on age, gender, and time elapsed from MI. Results indicated no significant differences in inflammatory markers between the depressed and nondepressed group.

Finally Shimbo, Rieckmann, Paulino, and Davidson (2006) examined the relationship between CRP and depression within 1 week of an acute coronary syndrome (ACS; i.e., recent MI or unstable angina) and then again 3 months later. Results suggested that CRP was not cross-sectionally associated with depression at baseline but was at 3 months post-ACS.

Although previous work addresses the hypothesis that inflammatory activity promoted by depression operates as a mechanism for recurrent CHD, it also has implications for the possibility that inflammatory activity promotes depression in MI patients. Support for the latter proposition would encourage the view that the development, progression, and clinical manifestation of CHD reflect bidirectional influences between inflammation and depression, as opposed to a simpler, unidirectional pathway. In addition, if inflammatory activity promotes depressive symptoms in heart patients, it may exacerbate the course of disease through depression-related behavioral mechanisms involving poor disease management, in addition to possible direct pathophysiological effects of depression (Evans et al., 2005).

Accordingly, the purpose of the present study was to determine whether the inflammatory markers IL-6 and IL-1β are prospectively associated with subsequent depressive symptomatology in acute MI patients. MI is associated with an overall increase in inflammatory activity (Balbay et al., 2001), and there is a high

prevalence of depression following MI (Lesperance, Frasure-Smith, & Talajic, 1996). Given these observations, and the capacity of inflammatory activity to produce depressive symptoms, we expected a prospective association between inflammatory markers in acute MI patients and depressive symptoms measured approximately 7 months later. A prospective association would be consistent with a possible causal relationship and would lend prognostic value to the biomarkers with regard to the subsequent mental state and behaviors of MI patients.

Methods

Participants

Participants were a convenience sample of 50 patients admitted to the Robert Wood Johnson University Hospital in New Brunswick, New Jersey, for an apparent MI. A total of 16 patients were lost during follow-up assessment, leaving a sample of 34 patients for longitudinal analyses. Patients were recruited between February 2002 and September 2003. All met the standard criteria for MI (Antman et al., 2000). Patients were excluded from the study if they did not have a diagnosed MI, were not proficient in English, or were infected with human immunodeficiency virus (HIV). Independent sample *t* tests and chi-square analyses were conducted to identify differences on any of the study variables between the patients who underwent follow-up assessment and those lost to follow-up. Results indicated that dropouts were more depressed at baseline compared with participants with complete data (*M*s = 13.8 and 6.4, respectively, $t = 2.82$, $df = 47$, $p < .01$). There were no other significant differences.

Procedure

The initial assessment took place in the hospital following admission for MI. Once informed consent was obtained, a questionnaire packet was administered and a blood sample was drawn. Samples were centrifuged to separate plasma from cells, stored immediately in a −70°C freezer, and thawed later for assay. Initial interviews were conducted in the hospital, as well as over the telephone during the first 2 weeks following discharge. Follow-up interviews were conducted by telephone approximately 7 months ($M = 217.0$ days, standard deviation [*SD*] = 26.1) following admission.

Measures

Psychological variables. The Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff & Teri, 1986) was used to measure depressive symptoms

at all three time points. The CES-D provides a continuous measure of depressive symptoms. For logistical reasons, it was not possible to administer the CES-D to all patients both in the hospital and over the telephone within 2 weeks of discharge. For patients who were given both measures ($n = 27$), hospital and telephone CES-D scores were significantly correlated ($r = .73$, $p < .0001$). Therefore, when both scores were available, the two values were averaged. In the remaining cases, either the hospital ($n = 9$) or 2-week postdischarge ($n = 14$) CES-D score was used, depending on which was available. Analyses using dummy variables to represent the three different sources of baseline CES-D scores (in the hospital, 2-week discharge, and their mean) indicated that this variation had no significant effect on the reported results.

For the baseline sample, 5 out of 50 patients had a history of depression as indicated by medical chart records. Of these patients, 3 were dropouts, leaving 2 in the longitudinal sample. Analyses using dummy variables to represent history of depression indicated that it had no significant effect on the reported results.

Biomarkers. Blood samples were drawn following venipuncture of a forearm vein, usually the basilic. IL-6 and IL-1β were quantified using commercially available high-sensitivity, enzyme-linked immunosorbent assays according to the manufacturer's instructions (Pharmingen Inc., 2003). These assays can effectively detect concentrations as low as 4 pg/ml. All assays were run in duplicate. The average coefficient of variance % (CV%) was acceptable for both biomarkers (IL6 CV% = 10.2%, IL1 CV% = 12.3%).

Medical chart data. Data were extracted from medical charts to characterize patients with regard to several factors related to coronary disease (i.e., known history of coronary artery disease, arrhythmias, hyperlipidemia, and previous MI). In addition, medical chart data provided information on other aspects of the patients' medical history that might influence inflammation and/or depressive symptoms (i.e., diabetes mellitus, peripheral vascular disease, history of congestive heart failure, history of renal failure, obesity [body mass index > 30], and malignancy). These conditions were coded (absent = 0, present = 1) and the resulting data summed to create an index of comorbidity.

Statistical Analysis

Pearson correlations were used to assess bivariate associations between the main predictor and outcome variables. Multiple regression analysis was used to examine inflammatory markers as multivariate predictors in separate analyses of baseline and 7-month follow-up measures of depressive symptoms. Because of the pronounced positive skew in the distribution of IL-6, IL-1β, and baseline

depressive symptoms, log transformations [log $(x + 1)$] were performed. Age, gender (male = 0, female = 1), ethnicity (non-White = 0, White = 1), and the comorbidity index were included in both regression models along with the biomarkers. Baseline depression was included as a predictor in the analysis of 7-month depressive symptoms, so that results for other predictors would reflect the effects on the change in depressive symptoms.

Results

Table 1 presents descriptive information for the sample. At admission, the patients' ages ranged from 29 to 79, with a mean of 56.8 years ($SD = 11.5$). There were 39 men (78%) and 11 women (22%). Forty participants were White (80 %). Patients were recruited in the hospital between 1 and 9 days following admission ($M = 3.9$).

Bivariate Associations

Table 2 presents bivariate associations. At baseline, IL-1β and IL-6 were significantly intercorrelated ($r = .35$, $p < .05$, $n = 50$). Baseline IL-6 was significantly associated with 7-month CES-D total scores ($r = .39$, $p < .05$, $n = 34$). There were no other significant bivariate relationships (ps > .21).

Regression Analyses

Table 3 presents the cross-sectional regression analysis of baseline data. Results indicated no significant associations between inflammatory markers and CES-D scores after controlling for demographics and comorbid conditions (ps > .20). No predictors were significantly associated with baseline CES-D scores.

Table 4 presents the prospective analysis for 7-month CES-D scores. Results indicated a significant effect for baseline IL-6 ($\beta = .60$, $p < .01$, $n = 34$). These results are depicted in Figure 1. There was a significant association between ethnicity and 7-month CES-D scores, such that Whites were less depressed than non-Whites ($\beta = .40$, $p < .05$, $n = 34$).[2] No other variables were significantly predictive of 7-month CES-D scores.

Discussion

Results of this study indicate a significant association between baseline IL-6 levels measured within 2 weeks of hospitalization for MI and depressive

[2]We reran this analysis with only the data for White participants ($n = 27$), and the results did not differ.

Table 1

Descriptive Statistics

	Sample	*N*	%	*M*	*SD*	Range
Demographics						
Age	BL			56.8	11.5	29–79
	PR			(58.9)	(11.7)	(31–79)
Gender						
Male	BL	38	78.0			
	PR	(28)	(82.4)			
Female	BL	11	22.0			
	PR	(6)	(17.6)			
Ethnicity						
White	BL	40	80.0			
	PR	(27)	(79.4)			
Non-White	BL	10	20.0			
	PR	(7)	(20.6)			
Depression scores						
Depressive symptoms (baseline)	BL			8.7	9.1	0–44
	PR			(6.3)	(5.5)	(0–20)
Depressive symptoms (7 months)	PR			(5.4)	(4.1)	(0–15)

Table 1

(Continued)

	Sample	*N*	%	*M*	*SD*	Range
Proinflammatory markers						
Interleukin-6 (pg/ml)	BL			120.7	293.5	.0–1,718.7
	PR			(104.3)	(56.2)	(.0–1,277.9)
Interleukin-1 (pg/ml)	BL			54.3	121.4	.0–542.4
				(69.1)	(142.2)	(.0–542.4)
Medical history						
History of coronary artery disease	BL	17	34.0			
	PR	(12)	(35.3)			
History of arrhythmias	BL	3	6.0			
	PR	(2)	(5.9)			
History of myocardial infarction	BL	11	22.0			
	PR	(6)	(17.6)			
Hyperlipidemia	BL	29	58.0			
	PR	(18)	(52.9)			
Body mass index (BMI)	BL			31.3	5.8	22.9–50.4
				(30.1)	(4.6)	(22.9–38.2)
Comorbidity index	BL			0.9	1.1	0–4
	PR			(1.1)	(1.0)	(0–4)

Note. Variables summed to create the comorbidity index were history of heart failure, diabetes mellitus, peripheral vascular disease, history of malignancy, obesity (body mass index > 30), and history of renal disease. Values inside parentheses represent descriptive statistics from the subsample of patients with both baseline and 7-month follow-up data.
BL = baseline sample; PR = prospective sample.

Table 2

Bivariate Associations Between Biomarkers and Depression Measures

Variables	Log IL-6 ($n = 50$)	Log depressive symptoms BL ($n = 50$)	Body mass index ($n = 50$)	Depressive symptoms FU ($n = 34$)
Log IL-1β	.346* $p = .0014$	.071 $p = .623$	−.039 $p = .790$	.139 $p = .434$
Log IL-6		−.127 $p = .380$	−.109 $p = .451$	.388* $p = .024$
Log depressive symptoms BL			.254^ $p = .076$	.217 $p = .218$
Body mass index				.261 $p = .136$

IL-1β = interleukin-1β; IL-6 = interleukin-6; BL = baseline; FU = follow-up.
^$p < .10$. *$p < .05$.

Table 3

Multiple Regression Analysis for Log Baseline Depressive Symptoms (n = 50)

Predictors	*B*	SE	β	sr^2	*p*
Age	−.006	.005	−.181	.033	.226
Gender	.145	.141	.156	.024	.312
White or non-White	.101	.145	.105	.011	.488
Comorbidity index	.071	.56	.185	.035	.215
Log interleukin-1β	.055	.070	.437	.014	.437
Log interleukin-6	−.104	.080	−.203	.038	−.201

Note. Values of *B* and β are raw and standardized regression coefficients, respectively. SE is the standard error for *B*. sr^2 is the squared semipartial correlation. For gender, 0 = male, 1 = female; for race, 0 = non-White, 1 = White. Variables summed to create the comorbidity index were history of heart failure, diabetes mellitus, peripheral vascular disease, history of malignancy, obesity (body mass index > 30), and history of renal disease. Model $R^2 = .130$.

Table 4

Multiple Regression Analysis for 7-Month Depressive Symptoms (n = 34)

Predictors	*B*	SE	β	sr^2	*p*
Age	–.023	.058	–.068	.004	.688
Gender	–1.797	1.883	–.171	.034	.349
White or non-White	–3.992	1.865	–.402*	.150	.042
Comorbidity index	.228	.674	.056	.003	.738
Log baseline depression	2.542	1.873	.226	.066	.186
Log interleukin-1β	–.021	.813	–.005	.000	.979
Log interleukin-6	3.447	1.142	.604**	.259	.006

Note. Values of *B* and β are raw and standardized regression coefficients, respectively. SE is the standard error for *B*. sr^2 is the squared semipartial correlation. For gender, 0 = male, 1 = female; for race, 0 = non-White, 1 = White. Variables summed to create the comorbidity index were history of heart failure, diabetes mellitus, peripheral vascular disease, history of malignancy, obesity (body mass index > 30), and history of renal disease. Model $R^2 = .333$.
*$p < .05$. **$p < .01$.

symptoms assessed approximately 7 months later. By contrast, baseline IL-1β levels were not prospectively associated with depressive symptoms, and neither IL-6 nor IL-1β was cross-sectionally associated with depressive symptoms measured at baseline. To our knowledge, this is the first study to report a prospective association between IL-6 and subsequent levels of depressive symptoms.

These results suggest that heightened levels of IL-6 may have long-term affective, cognitive, and/or behavioral effects. The linkage between baseline IL-6 and subsequent depressive symptoms can plausibly involve either a prolonged IL-6 response that maintains the depressive symptoms or a pathway in which IL-6 initiates other processes that, in turn, have a long-term influence on depressive symptomatology. Unfortunately, data to evaluate either of these possibilities were not available in the present study.

Although our findings are consistent with the hypothesis that sustained IL-6 elevations come to maintain depression directly over time, this may be less likely than other pathways because IL-6 was not initially related to depressive symptoms. In this respect, our study is in accord with previous evidence suggesting there is no cross-sectional association between cytokines and depressive symptoms in acute CHD patients (Annique et al., 2005; Lesperance et al., 2004; Miller, Freedland, & Carney, 2005). There are two studies that have found a link

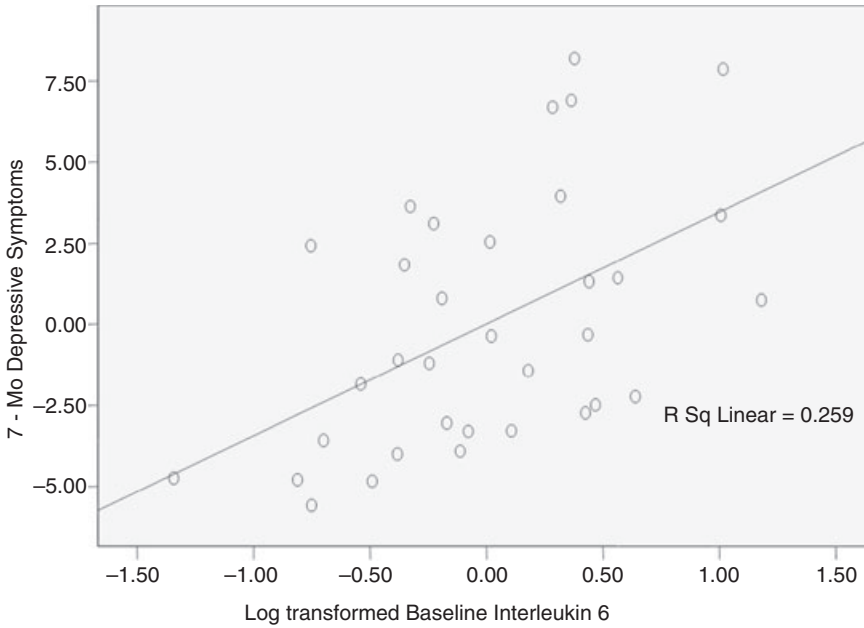

Figure 1. Partial regression plot: Interleukin-6 predicting 7-month depressive symptoms. *Note*. The above graph is a partial regression plot; therefore, values on the *x* and *y* axes are not indicative of actual values for either interleukin-6 or depression, respectively. The scores above indicate the unique influence of interleukin-6 on depressive symptoms 7 months later after controlling for age, gender, ethnicity, and comorbidity issues (history of heart failure, diabetes mellitus, peripheral vascular disease, history of malignancy, obesity, and history of renal disease).

between IL-6 and vital exhaustion (Appels et al., 2000; Janszky et al., 2005), but only one of these also linked cytokines with depression (Appels et al.), and this was in patients referred for coronary angioplasty, a sample that differs from that of the present study comprising patients hospitalized for MI.

If IL-6 is not directly responsible for sustained elevations in depressive symptoms, it remains possible that other inflammatory markers known to be influenced by IL-6, such as CRP, can play this role because they have been linked to depression cross-sectionally (Lesperance et al., 2004; Miller, Freedland, Duntley, et al., 2005). In this regard, the temporal pattern reported by Shimbo et al. (2006) is of interest. As noted earlier, CRP concentrations were not cross-sectionally associated with depression soon after an ACS, but they were cross-sectionally associated with depression 3 months post-ACS in the same patients. These results, taken together with those of the present study, are

highly consistent with the hypothesis that baseline IL-6 promotes increased concentrations of CRP after an MI, which, in turn, may promote depressive symptomatology. This theoretically plausible pathway warrants empirical examination.

There are other pathways that might mediate a relationship between initial IL-6 levels and subsequent depression. One is the hypothalamic–pituitary–adrenocortical (HPA) axis. It has been shown that IL-6 stimulates the secretion of corticotropin-releasing factor, which plays a central role in HPA axis activation and subsequent cortisol release (Connor & Leonard, 1998; Corcos, Guilbaub, Hjalmarsson, Chambry, & Jeammet, 2002; Obrien, Scott, & Dinan, 2004). Baseline levels of cortisol during times of low stress have been found to be elevated among depressed patients, suggesting heightened HPA activity (Plotsky, Owens, & Nemeroff, 1998). A central regulatory system for the HPA axis involves glucocorticoid receptors in the brain, which respond to heightened levels of cortisol by sending subsequent signals to reduce HPA activity (van Praag, 2004). Among depressed patients, this feedback system does not function properly to down-regulate HPA activity (van Praag). As stated earlier, IL-6 impacts increased cortisol activity. Based on this, it is plausible that IL-6 initiates a cortisol response that, over time, becomes poorly regulated, resulting in subsequent depressive symptoms, through a glucocorticoid receptor-mediated disruption of neuronal integrity, and potential degeneration in critical brain regions, such as the hippocampus. Whether elevations of IL-6 contribute to this is not well understood. Still another possible pathway involves serotonergic neural circuits. IL-6 has been found to reduce the levels of serotonin both within the brain and in the periphery (Connor & Leonard; Corcos et al.; Obrien et al.). Serotonergic dysfunction is thought to be associated with depressive symptoms, and serotonin reuptake inhibitors are effective in the treatment of depression (Williams et al., 2000). These pathways also warrant empirical examination.

Although not specifically anticipated, the contrasting results for IL-1β and IL-6 might be explained in terms of known physiological processes. IL-1β is thought to be one of the primary activators of the inflammatory cascade (Dantzer, 2002). It is believed to be one of the first cytokines to be activated during the acute phase response and is thought to promote the production of other cytokines, such as IL-6 (Reyes & Coe, 1998). Subsequently, IL-1β is down-regulated by other cytokines, including IL-6 (Xing et al., 1998), which is thought to have a longerasting effect on inflammatory processes, including the production of acute phase proteins (e.g., CRP), HPA activity, and the reduction of serotonin (Connor & Leonard, 1998; Corcos et al., 2002; Obrien et al., 2004). Based on this line of reasoning, it is plausible to suggest that, because of the role that IL-6 plays in long-term inflammatory regulation, IL-6 will have a slowly developing and sustained effect on depressive symptoms. Additional research is needed to evaluate this suggestion.

Methodological factors may have influenced the results of this study. The small convenience sample limits both generalizability and statistical power. In addition, there was no comparison group to permit more direct examination of the effects of MI. Moreover, as noted above, blood samples were collected from a forearm vein, making it impossible to determine the source of the inflammatory markers. There also was a small but significant difference between the level of depressive symptoms between those in the full sample and those lost during follow-up. Although this limits the generalizability of results, it may also introduce a conservative bias that worked against obtaining evidence of larger associations. In other words, the significant prospective relationship that was detected between IL-6 and 7-month depressive symptoms was detected despite what is very likely an attenuation of range in the follow-up depression measure. Finally, baseline interview and biomarker data were collected at slightly different time points, which may have weakened the cross-sectional associations between measures of depression and inflammation and, because biomarker data were not available at the time of the 7-month follow-up, it was not possible to examine the time course of inflammatory activity in relation to changes in depressive symptoms.

Despite the limitations, the present findings have potentially important implications. Depressive symptoms in heart patients are associated with poor quality of life (Goyal, Idler, Krause, & Contrada, 2005), suboptimal disease management (Carney, Freedland, Eisen, Rich, & Jaffe, 1995), and failure to enact health-promoting lifestyle changes (Ziegelstein et al., 2000). These and other effects of depression appear to increase the risk of disease progression and cardiovascular mortality (Penninx et al., 2001). The prognostic significance of depression, together with the evidence for a central role of inflammatory processes in coronary disease, underscores the need to document and identify the basis of associations between cytokines and depressive symptoms. Our results indicate that IL-6 may have long-term effects on depressive symptomatology. It has been speculated that depression and inflammatory processes may promote one another in cardiac patients in a positive feedback mechanism (Miller, Freedland, Duntley, et al., 2005). Therefore, the long-term effects of IL-6 warrant additional attention as a factor contributing to the psychological, behavioral, and cardiovascular consequences of depression in heart patients.

Mechanism-focused work has shed light on the relationship between traditional antidepressive medications and cytokine-induced depression (Capuron, Hauser, Hinze-Selche, Miller, & Neveu, 2002). It has also generated findings suggesting the potential utility of endogenous anti-inflammatory agents for reducing depression (Capuron et al.), although this evidence is still preliminary. Further clarification of these issues, and the development of new, effective therapies for comorbid depression and coronary disease, will require a combination of basic and clinical research strategies.

Conclusions

Following MI, IL-6 may play a long-term role in sustaining depression. Likely pathways for those changes involve IL-6 itself, CRP, the HPA axis, and/or serotonergic neural circuits. More work is needed to document and explicate the link between IL-6 and depression in MI patients, which ultimately may inform efforts to design effective interventions in this population.

Acknowledgment

This research was supported by a grant from the Charles A. Dana Foundation.

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