Depressive Symptoms and Lymphocyte Proliferation in Older Adults

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In an 18-month prospective study, community-dwelling older adults, including both spousal caregivers of dementia patients and noncaring giving controls, were examined. Participants were selected on the basis of the presence or absence of chronic depressive symptoms that exceeded a cutoff score for clinically relevant depressive symptoms on a self-report symptom measure. Compared with nondepressed older adults, those with chronic, mild depressive symptoms had poorer T cell responses to 2 mitogens from baseline to follow-up. Additionally, among individuals with depressive symptoms, older age was associated with the poorest blastogenic response to the mitogens at follow-up. These findings extend the association between depression and immune function to community-dwelling older adults with chronic, mild depressive symptoms.

The possible interaction of age and depressive symptoms on immune function is significant because older adults may be more vulnerable to adverse immunological changes, they may be slower to recover from immunological alterations, and they may be more likely to experience negative health consequences as a result of immune dysregulation (Coe, 1993; Rabin, 1999). Major depression is reliably associated with a variety of changes in immune function (Herbert & Cohen, 1993); both age and inpatient hospitalization status, one index of severity, may influence the association between major depression and immune function. Among studies primarily involving inpatients (Herbert & Cohen, 1993), reliably stronger effects have been found for older clinically depressed participants (age 44 to 71 years) than for younger participants (age 29 to 42 years). A classic study by Schleifer, Keller, Bond, Cohen, and Stein (1989) suggested that both age and hospitalization status were important for the association between major depression and immune function; older depressed inpatients showed decreased mitogen responses compared with nondepressed controls, whereas there were no age-related changes for depressed outpatients.

In contrast to these inpatient studies, research focused on clinically depressed outpatients has provided mixed results. A recent well-controlled study found poorer lymphocyte proliferative responses in unmedicated outpatient women being treated for mild to moderate major depression compared with nondepressed controls (Miller, Cohen, & Herbert, 1999). Older depressed women (age 40 to 48 years) showed poorer natural killer (NK) cell lysis (an in vitro measure of the ability of NK cells to destroy tumor cells) compared with lysis in younger depressed women (age 22 to 39 years).

Although the association between major depression and immune function has been investigated, the relationship between subthreshold depressive symptoms and immune function in older adults has not been well examined. Subthreshold depressive symptoms in nonhospitalized adults have been associated with poorer NK cell lysis in young (Heisel, Locke, Kraus, & Williams, 1986) and older (Irwin, Daniels, Bloom, Smith, & Weiner, 1987) adults, poorer lymphocyte proliferation to phytohemagglutinin (PHA) in middle-aged adults (Linn, Linn, & Jensen, 1984), and increases in plasma interleukin (IL)-6 in older adults (Dentino et al., 1999; Lutgendorf et al., 1999); these findings remain even when health status and behaviors are controlled. The level of depressive symptoms across these studies has been mild to moderate, and only two studies have reported clinically relevant depressive symptoms that exceeded a cutoff on a self-report measure (Dentino et al., 1999; Linn et al., 1984). Additionally, the majority of these investigations have been cross-sectional, and the potential role of age in the association between depressive symptoms and immune function has not been examined.

Determination of the relationship among age, depressive symptoms, and immune function in older adults is important. Depressive symptoms that do not meet the threshold for major depression may be as high as 12%–20% among older adults (Penninx et al., 1999; Unutzer et al., 1997), and significant psychosocial impairment has been associated with subthreshold depression (Lewinsohn, Seeley, Solomon, & Zeiss, 2000). Increased morbidity and mortality associated with depressive symptoms further support the clinical significance of subthreshold depression, particularly for older adults (Penninx et al., 1999).

The majority of research addressing the association between depressive symptoms and immune function has been cross-
sectional, and few immune studies have focused on nonhospitalized older adults with mild depressive symptoms. The relative inattention to longitudinal studies of immune function in dysphoric older adults is noteworthy given that as many as 15% to 57% of community-dwelling older adults have been found to experience chronic depressive symptoms over a 4-year period (Robinson-Whelen, Tada, MacCallum, McGuire, & Kiecolt-Glaser, 2001). In the current study, we evaluated one potential physiological consequence of such chronic depressive symptoms: lymphocyte proliferation to mitogens provides a model of the body’s response to infectious agents, such as bacteria or viruses (Reinherz & Schlossman, 1980), and decreased lymphocyte proliferation has been associated with a number of health outcomes, including recovery from surgery (Linn & Jensen, 1983), morbidity, and mortality (Murasko, Gold, Hessen, & Kaye, 1990). We examined community-dwelling spousal caregivers and noncaregiving controls. We hypothesized that participants with chronic depressive symptoms would have poorer T cell proliferation to mitogens over an 18-month period compared with nondepressed adults and that the oldest dysphoric adults would show the poorest proliferative responses.

Method

Participants and Procedure

Participants were part of a larger longitudinal study on stress and health in community-dwelling older adults that included spousal caregivers of dementia patients and noncaregiving controls. Caregivers were recruited from local dementia evaluation centers, neuropsychologist’s referrals, the local Alzheimer’s Disease and Related Disorders Association (ADRDA) support groups and newsletter, respite care programs, and governmental caregiver support programs. Noncaregivers were recruited through newspaper advertisements, church groups, notices posted in senior citizen centers, and referrals from other participants. Participants were excluded if they had major immunologically related health problems, such as cancer or recent surgeries.

For the current study, older adults who completed psychological measures and blood draws at the time of the baseline and 18-month follow-up assessments and reported the presence versus absence of chronic depressive symptom levels were selected for participation. Depressive symptom levels were evaluated using a cutoff score for clinical relevance on a self-report measure. Our selection criterion of presence versus absence of chronic depressive symptom levels resulted in the exclusion of 13 adults who changed from nondepressed to depressed from baseline to follow-up and 16 adults who changed from depressed to nondepressed from baseline to follow-up. Prior studies have used varying approaches for defining clinically relevant depression caseness (see, e.g., Lewinsohn et al., 2000). In the current study, caseness included clinically relevant depressive symptoms that exceeded a cutoff score on a self-report measure whether or not the symptom level met formal diagnostic criteria for major depression or dysthymia. Nondepressed participants \((n = 56)\) did not meet criteria for clinically relevant symptoms, and depressed participants \((n = 22)\) reported chronic depressive symptoms.

There was no significant difference in age between the nondepressed \((M = 72.04 \text{ years}, SEM = 0.94)\) and depressed \((M = 74.32, SEM = 1.57)\) participants. The majority of participants were Caucasian \((89\% \text{ of the nondepressed and } 100\% \text{ of the depressed group})\). In both groups, \(64\% \text{ were female. There were no significant differences between groups in marital status (71\% of nondepressed and 86\% of depressed participants were married), education level (61\% of nondepressed and 73\% of depressed participants had some college or greater), or annual income (72\% of nondepressed and } 59\% \text{ of depressed participants received } $20,000 \text{ or more). The nondepressed group included 25 caregivers (45\%) and 31 noncaregivers (55\%), and the depressed group included 15 caregivers (68\%) and 7 noncaregivers (32\%). Among the caregivers in the nondepressed group, \(56\% (n = 14)\) were current caregivers, and \(44\% (n = 11)\) were former caregivers whose spouse had died. Among the caregivers in the depressed group, \(80\% (n = 12)\) were current caregivers and \(20\% (n = 3)\) were former caregivers. The average number of years spent caregiving did not differ between the nondepressed and depressed groups \((M = 6.53, SEM = 0.65, \text{ and } M = 6.02, SEM = 1.26, \text{ respectively})\).

Participants completed psychological measures following blood draws at baseline and 18-month follow-up. Blood was drawn between 8:00 and 10:00 a.m., to control for diurnal variations.

Measures

Depression. The nondepressed and depressed groups were constructed using participants’ report of depressive symptoms on the short form of the Beck Depression Inventory (BDI–SF) at baseline and follow-up (Beck & Beck, 1972). The BDI–SF, a 13-item measure that provides information on the severity of affective and cognitive depressive symptoms over the past week, correlates highly with the total score of the 21-item BDI \((r = 0.96)\) and with clinician’s ratings of depression \((r = 0.61; \text{ Beck & Beck, 1972})\). BDI–SF scores in the range of 0 to 4 demonstrate no or minimal depression, scores in the 5 to 7 range demonstrate mild depression, scores in the 8 to 15 range demonstrate moderate depression, and scores greater than 15 demonstrate severe depression (Beck & Beck, 1972).

Using a sample of older adults receiving outpatient treatment for depression and older adult nondepressed controls, Scogin, Beutler, Corbishley, and Hamblin (1988) found acceptable internal reliability and criterion group validity for the BDI–SF; a cutoff score of 5 differentiated depressed and nondepressed older adults. This cutoff score has since been used as a threshold for clinically relevant depressive symptoms in other studies (see, e.g., Kissane et al., 1996). In the current study, a cutoff score of 5 was used to identify clinically relevant depressive symptoms. Participants who scored 5 or greater on the BDI–SF at both baseline and follow-up were categorized in the chronic depressive symptoms group (i.e., the depressed group), whereas participants in the nondepressed group scored 4 or less at both time points. Cronbach’s \(\alpha\) for the BDI–SF in the current study was .87 and .84 at baseline and follow-up, respectively.

Further information about current depression was obtained using the Structured Clinical Interview for DSM–III–R Disorders, nonpatient version (SCID–NP; Spitzer, Williams, Endicott, & Gibbon, 1987) at baseline and 1 year later. Audiotaped interviews were randomly selected for 20% of the participants, to examine interrater reliability for SCID–NP diagnoses. The kappa coefficients were .78 and .92 for affective disorders at baseline and follow-up, respectively.

Chronic health problems. Participants completed the Older Adults Resources Survey (Fillenbaum & Smyer, 1981), a self-report measure that assesses the presence of 25 chronic health problems, at baseline. The number of items endorsed was summed and used as a covariate in analyses. Additionally, due to recent evidence linking depression and cardiovascular disease (Rozanski, Blumenthal, & Kaplan, 1999), the possible association between cardiovascular-related disorders, depressive symptoms, and lymphocyte proliferation was examined.

Immunological assays. Participants were tested in mixed groups across the year, so that blood was simultaneously collected from both groups throughout the study. In the larger longitudinal study, approximately 50 ml of blood was collected from participants at each blood draw, and 10 ml of blood was used to complete the lymphocyte proliferation assays included in the current study. (No other immune data have been reported on this cohort of participants.) The same lots of mitogen were used across the year, so that blood was simultaneously collected from both groups. Participants completed psychological measures following blood draws at baseline and 18-month follow-up. Blood was drawn between 8:00 and 10:00 a.m., to control for diurnal variations.

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Participants in the depressed group was mild (50%) to moderate (41%), and no participants were taking antidepressant medication. The SCID–NP at baseline and follow-up identified the same 5 participants in the depressed group as having major depression or depression not otherwise specified, and 5 participants with dysthymia. There was no significant difference in BDI–SF depressive symptoms at baseline or follow-up between participants in the depressed group with $M = 9.40$, $SEM = 1.22$ at baseline; $F(1,70) = 8.60$, $SEM = 0.83$ at follow-up) and without $M = 8.00$, $SEM = 1.09$ at baseline; $M = 7.17$, $SEM = 0.46$ at follow-up) a clinical diagnosis of depression ($p > .1$).

Data Analyses

To facilitate comparisons between baseline and follow-up assays, $z$ scores were calculated for PHA and Con A blastogenic response data at baseline and follow-up; $z$ scores were used in repeated measures regression models (SPSS, 2000) to evaluate whether nondepressed and depressed participants differed in their relative positions in the distribution of blastogenic response to mitogens from baseline to follow-up. Immune function analyses involved continuous (age) and fixed (depression group) independent variables and repeated measures of dependent variables (the three concentrations of mitogens at baseline and follow-up). Repeated measures regression models are generalizations of the standard multiple regression model to include repeated measures of dependent variables (Keppel & Zedeck, 1989) and are analogous to analysis of variance (ANOVA). Additional analyses included Student’s $t$ test, general linear model ANOVA, and chi-square tests.

Outcomes are first presented for the nondepressed and depressed groups comparison, followed by the assessment of the influence of clinically diagnosed depression and caregiver status. Potential caregiver effects within and between the depressed and nondepressed groups were analyzed for BDI–SF scores and lymphocyte proliferation. Analyses were repeated using two different constructions of the caregiver group: the combination of current and former caregivers and solely current caregivers. There were no significant effects of caregiver status, regardless of the grouping method used, for severity of depressive symptoms ($p > .10$) or lymphocyte proliferation ($p > .40$). Similarly, there were no significant effects for length of time spent caregiving or severity of dementia-related behaviors. Thus, the remainder of the article focuses on the depression groups.

Results

Depression

In keeping with our selection criteria, the nondepressed group had significantly lower BDI–SF scores at baseline and follow-up (scores ranged from 0 to 4) compared with the depressed group (scores ranged from 5 to 18 at baseline and 5 to 13 at follow-up). Analyses specifying BDI–SF scores as the dependent variable and depression group, age, and gender as independent variables found significantly greater depressive symptoms in the depressed group ($M = 8.64$, $SEM = 0.81$ at baseline; $M = 7.82$, $SEM = 0.47$ at follow-up) compared with the nondepressed group ($M = 1.60$, $SEM = 0.17$ at baseline; $M = 1.54$, $SEM = 0.17$ at follow-up) at baseline, $F(1, 70) = 5.58$, $p = .02$, $\eta^2 = .08$, and follow-up, $F(1, 70) = 16.82$, $p < .001$, $\eta^2 = .19$. There were no significant effects for gender, but age showed significant main and interaction effects at follow-up, $F(1, 70) = 4.72$, $p = .03$, $\eta^2 = .06$, and $F(1, 70) = 7.88$, $p = .006$, $\eta^2 = .10$, respectively. However, Pearson product–moment correlations between age and BDI–SF scores at follow-up suggest weak relationships (for the total group of participants, $r = .10$, $p = .40$; for the nondepressed participants, $r = .13$, $p = .33$; for the depressed participants, $r = -.35$, $p = .11$).

The severity of the chronic depressive symptoms among participants in the depressed group was mild (50%) to moderate (41%), and among the nondepressed group was mild (50%) to moderate (39%).
significant effects for gender or clinically diagnosed depression. Because health behaviors can have direct effects on immune function (Kiecolt-Glaser & Glaser, 1988) we assessed smoking, caffeine intake, alcohol intake, sleep, nutrition, exercise, and medication use at baseline; we found no main or interaction effects on lymphocyte proliferation.

Discussion

This prospective study found that community-dwelling older adults with chronic, mild depressive symptoms had poorer lymphocyte proliferation to two mitogens from baseline to 18-month follow-up compared with nondepressed older adults. These findings are particularly notable in view of the mild levels of depressive symptoms among participants in the depressed group. All participants in the depressed group exceeded a cutoff score for clinically relevant depressive symptoms on a self-report measure at baseline and follow-up, but fewer than half of the participants met formal diagnostic criteria for depression.

Participants in the depressed group with and without a clinical diagnosis of depression did not significantly differ in the severity of their depressive symptom scores on the BDI–SF or in lymphocyte proliferation. This similarity between depressed participants with and without a clinical diagnosis of depression may result from our selection of participants with chronic rather than time limited, depressive symptoms. Alternatively, the similarity could be due to a restriction of depression severity scores within the mild range among our participants or to our sample sizes and coincident statistical power. Although we did not find strong support for an association between a continuous measure of depressive symptoms and lymphocyte proliferation, our results based on group comparisons did lend support to current studies of the clinical meaningfulness of mild depressive symptoms (Flett, Vredenburg, & Krames, 1997; Lewinsohn et al., 2000).

In the current study, the combination of chronic depressive symptoms and older age was associated with the poorest lymphocyte proliferation over an 18-month period. Schleifer et al. (1989) showed an interaction between aging and depression on immune function in a broad age range of adults hospitalized for major depression. The current study also found an interaction between age and depressive symptoms on immune function, but among

### Table 1

<table>
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<tr>
<th>Mitogen</th>
<th>Nondepressed M</th>
<th>Nondepressed SEM</th>
<th>Depressed M</th>
<th>Depressed SEM</th>
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<td>Baseline Con A μg/ml</td>
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<td></td>
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<tr>
<td>2.5</td>
<td>34,133.32</td>
<td>2,023.56</td>
<td>33,845.28</td>
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<td>1,482.15</td>
<td>23,141.32</td>
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<tr>
<td>Follow-up Con A μg/ml</td>
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<td>0.25</td>
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<td>0.01</td>
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<tr>
<td>PHA μg/ml</td>
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<tr>
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<td>0.41</td>
<td>0.01</td>
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Note. Con A = concanavalin A; PHA = phytohemagglutinin. Values were transformed into z scores before analyses. Mitogen concentration level was a within-subjects dependent variable in the repeated measures regression models. Separate analyses of the individual concentration levels of mitogen found statistically significant Time × Group and Time × Group × Age effects for the 5 μg/ml and 10 μg/ml PHA concentrations and the 2.5 μg/ml and 5 μg/ml Con A concentrations.

a Measured in counts per minute and log transformed before analyses.
b Measured in optical density.
community-dwelling adults with a restricted older age range and with chronic, mild depressive symptoms. In our study, the effect of age was not a function of severity of depressive symptoms; relatively younger and older depressed participants did not significantly differ in BDI–SF scores.

Why might there be a shift in lymphocyte proliferation over an 18-month period among older adults with chronic, mild depressive symptoms? The data from this and other studies suggest depressive symptoms may exacerbate and accelerate the immunological declines that typically accompany aging. Immune senescence occurs with aging, with the most consistent decrements occurring in cell-mediated immunity, particularly T cell function (Burns & Goodwin, 1990). Changes in the immune response, including dysregulation of the proinflammatory cytokines IL-2 and IL-6, and in endocrine function have been shown to occur within adults older than 60 years (Hamerman, 1999; Lamberts, van den Beld, & van der Lely, 1997; Mysliwska, Bryl, Foerster, & Mysliwski, 1998).

Of particular relevance for the findings of the current study, IL-2 is important for T cell regulation and lymphocyte proliferation (Rabin, 1999), and IL-6 can stimulate the hypothalamic–pituitary–adrenal axis leading to endocrine dysregulation and immunosuppression (Dentino et al., 1999; Ershler & Keller, 2000). Depression has also been associated with dysregulation of proinflammatory cytokines (Dentino et al., 1999; Lutgendorf et al., 1999) and endocrine function (Rozanski et al., 1999). Thus, immune and endocrine dysregulation associated with depression is similar to what is found in typical aging, suggesting that chronic dysregulation of these systems associated with depressive symptoms may actually age the immune response more rapidly.

Applying these findings to the current study, it appears that over an 18-month period, immune and endocrine dysregulation associated with both typical aging and chronic depressive symptoms interacted to produce a significant decline in lymphocyte proliferation among older adults experiencing depressive symptoms. It is plausible that other variables in addition to aging, and perhaps associated with aging, contributed to the significant changes we found. One such variable could be social support; the quantity and quality of social support have been associated with depression and immune function (Uchino, Cacioppo, & Kiecolt-Glaser, 1996). It is possible that age-related reductions in immune function may be exacerbated by the negative impact of depressive symptoms on seeking or maintaining social support, resulting in an acceleration of negative physiological outcomes.

An association among older age, depressive symptoms, and altered lymphocyte proliferation may have important health consequences. Prospective studies of healthy, independently living older adults have found increased rates of morbidity and mortality associated with poorer lymphocyte proliferation (Murasko, Gold, et al., 1990), and age-related changes in cell-mediated immunity may be associated with the increased risk and severity of infectious illness and cancer found in older adults (Burns & Goodwin, 1990). Relatively small alterations in immune function in older adults have been associated with increased vulnerability to infectious disease and poorer wound healing (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Kiecolt-Glaser, Murchu, Malarkey, Mercado, & Glaser, 1995). These negative outcomes may be exacerbated by depressive symptoms that accelerate age-typical immune dysregulation.

Some study characteristics potentially limit the generalizability of our results. Our findings are derived from participants selected for the presence or absence of chronic depressive symptoms. The degree to which similar associations would be found in episodic or more severe levels of depressive symptoms requires further investigation. Our participants included spousal caregivers of dementia patients and noncaregiving controls. Although we did not find any main or interaction effects for caregiver status, the physiological consequences of chronic depressive symptoms in the context of the chronic stress of caregiving may differ from non-caregiving contexts. Although we cannot completely rule out the possibility that the Group × Time effect was related to the assay procedures, we think it is unlikely. As noted earlier, previous studies from other laboratories and our own internal analyses provide strong evidence of the comparability of the assay procedures. Additionally, we removed the effects of differing measurement units of the assay procedures by using z scores.

This prospective study extends the association between depression and lymphocyte proliferation to community-dwelling older adults with chronic, mild depressive symptoms. Our findings suggest that detection and treatment of such symptoms may be important for optimal immune function in older adults. Clinically relevant mild depressive symptoms can be persistent (Robinson-Whelen et al., 2001; Unutzer et al., 1997), and in the current study, we found negative consequences on lymphocyte proliferation over an 18-month period. Although the prevalence of depressive symptoms may be high in older adults, these symptoms are often undetected and untreated (Hirschfeld et al., 1997). In accord with related work (Lutgendorf et al., 1999; Miller et al., 1999), our findings suggest that failure to address chronic, mild depressive symptoms in older adults has important negative physiological consequences.

References


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