Physical Illness and Depression in Older Adults
A Handbook of Theory, Research, and Practice

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Depression, Immune Function, and Health in Older Adults

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In this chapter, we summarize research on the relationships among age, depression (or depressed mood), and immune function in older adults. These studies suggest that depression, stress, and an immune system declining naturally with age yield greater down-regulation of immune function among older than younger adults. Therefore, we consider possible physical health consequences, with an emphasis on recent work addressing vaccine responses and wound healing. We also include a discussion of the implications for recovery from surgery, rates of infectious illness, and general physical well-being.

DEPRESSION AND IMMUNE FUNCTION

Major depressive disorder (MDD) has been associated with decrements in immune function in a variety of adult populations; however, this effect has not been as well explored among the elderly. Existing evidence suggests that declines in immune function may actually be larger among distressed older adults than younger individuals because of the added complications of an age-impaired immune system (Herbert & Cohen, 1993a; Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Schleifer, Keller, Bond, Cohen, & Stein, 1989).

Immunological research reviewed in this chapter refers to two common assessment methods: quantitative and qualitative assays (Kiecolt-Glaser & Glaser, 1988). Quantitative assays identify the percentage and number of specific types of lympho-

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cytes. For example, one technique employs monoclonal antibodies bound to fluorescent dyes to detect specific surface proteins on lymphocytes. The percent of cells that fluoresce can be measured by a flow cytometer yielding a count of the specific cells being investigated. By obtaining a differential blood count, one can also determine the absolute number of each subpopulation of cells. However, such quantitative assays may be difficult to interpret because the number of circulating immune cells may have little correlation with the protective capabilities of the cells (Herbert & Cohen, 1993b).

Qualitative measures are more strongly associated with psychological stressors than are quantitative measures (Kiecolt-Glaser & Glaser, 1995); one type of qualitative (or functional) assay is blastogenesis, which assesses lymphocyte proliferation in response to stimulation by a mitogen (Kiecolt-Glaser & Glaser, 1995; O’Leary, 1990). Lymphocytes are generally found in a resting condition, but they become activated when in contact with an infectious agent and reproduce to combat the infection. Blastogenesis provides a way to assess this proliferation in a laboratory setting. Mitogens are added to media in which peripheral blood lymphocytes are cultured to induce proliferation in vitro; two common T-cell mitogens are phytohemagglutinin (PHA) and concanavalin A (Con A), which each target different subsets of lymphocytes. Radioactive isotopes are included in the media, and when the cells divide, the isotope is incorporated into cellular DNA. Proliferation can be quantified by measuring the amount of radioactive emission expressed as counts per minute. Interestingly, both enumerative and functional immune assays show depression-associated declines in elderly subjects (Herbert & Cohen, 1993a); however, age-related immune declines are more notable among functional assays.

Clinical depression is correlated with a decrease in the number of several leukocyte subsets. For example, elderly depressed women had fewer total T lymphocytes and T helper cells than elderly nondepressed women (Targum, Marshall, Fischman, & Martin, 1989). In another study, community subjects without a history of depression had more T suppressor cells associated with aging, while unipolar depressed patients did not show a comparable response (Schleifer et al., 1989). These data provide evidence of differences in immune cell numbers between depressed and nondepressed older adults. However, to be included in this latter study, elderly subjects could not be taking any medication, a criterion that may have selected for those in exceptionally good health, thus producing a nonrepresentative sample.

Not only are there dissimilarities in cell number between depressed and nondepressed older adults, but there are also studies that suggest differences in the qualitative aspects of immune function; a meta-analysis suggested that there were reliable variations among depressed elderly subjects compared to nondepressed peers (Herbert & Cohen, 1993a). Proliferative responses to three mitogens, phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed, as well as natural killer (NK) cell activity, showed moderate effect sizes for depression. Mitogen-induced lymphocyte proliferation, or blastogenesis, is an in vitro assay of cell function that examines the ability of cells to replicate when stimulated. NK cell activity, determined by a measurement of target cell killing or lysis, is an important antiviral and antitumor defense (Kiecolt-Glaser & Glaser, 1995).

Severity of depression may be related to qualitative differences in immune function between depressed and nondepressed subjects (Schleifer et al., 1989). For example, elderly participants with higher scores on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) and the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) had lower T-lymphocyte responses to mitogen stimulation than those who were less depressed (Darks et al., 1988). Participants having MDD with melancholic features, or psychotonic depressives, showed lower lymphocyte responses to PHA and pokeweed than those with minor depression (Maes, Bosmans, Suy, Minner, & Raus, 1989). Thus, changes in immune function may become more problematic as the severity of depression increases.

Two proposed pathways link depression and down-regulation of the immune system: neuroendocrine and behavioral (Herbert & Cohen, 1993a). Support for neuroendocrine mediation comes from work showing activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) in depressed patients versus nondepressed controls (Ritchie & Nemeroff, 1991; Stokes, 1987). Both cortisol and catecholamines can have adverse effects on immune cells that have receptors for these hormones (Rabin, Cohen, Gargul, Lysle, & Cunnick, 1989). Modulation of the immune system via the neuroendocrine pathway has received some empirical support in studies that have linked depression to increases in cortisol, as well as further work showing that elevations in cortisol can down-regulate the immune system. Unfortunately, studies incorporating all three elements simultaneously have not provided convincing evidence for this mechanism. However, there are two methodological reasons that may explain this difficulty: an overreliance on depressed populations has restricted the range of cortisol data available, and single cortisol assessments in many studies have limited the assessment of cortisol variability (Herbert & Cohen, 1993a).

Changes in health behaviors provide a second pathway for depression-associated immune down-regulation (Kiecolt-Glaser & Glaser, 1988). Compared to their nondepressed counterparts, those suffering from depression exercise less, sleep less, maintain poorer diets, and engage in greater use of cigarettes, alcohol, and other substances (Grunberg & Baum, 1985). Indeed, there is ample evidence that these behaviors can alter immune function (Friedman, Klein, & Specter, 1991; Irwin, Smith, & Gillin, 1992; Simon, 1991). Thus, the health habits of depressed older adults may also contribute to the observed changes in immune function.

Although many studies have found immunological differences between depressed and nondepressed samples, not all investigations find support for such a relationship (e.g., Brambilla, Maggioni, Cenacchi, Sacerdote, & Panerai, 1993). Perhaps depression-related decrements in immune function are not inevitable; some individuals may be more susceptible than others. Even among the aged, diminished function is not uniform. It is thus important to examine what factors best predict changes in immune function, and which individuals are at greatest risk.

STRESS AND IMMUNE FUNCTION

Although syndromal depression is associated with diminished immune function, meeting criteria for clinical depression is not a necessary condition for immune change; individuals undergoing stressful life experiences may also be at risk. A meta-analysis of stress and immune function revealed significant effect sizes for several immune parameters including stress-related increases in the number of white blood cells, and
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may also differ between chronically stressed caregivers and their noncaregiving peers (Glaser & Kiecolt-Glaser, 1997). In comparisons between 71 family caregivers and 58 noncaregivers, caregivers had higher antibody levels to latent HSV-1 and poorer HSV-1-specific T cell responses; however, there were no significant differences in neutralizing antibody titers between groups. These data support the hypothesis that psychological stress may alter the immune system’s control over herpesvirus latency.

Delayed hypersensitivity skin tests also differentiated spousal caregivers and noncaregiving participants (McCann, 1991). Used to assess cell-mediated immune responses in the body, delayed hypersensitivity skin test reactions are provoked by placing sensitizing chemicals under the participants’ skin (Brock & Madigan, 1991). In healthy individuals with an intact immune system, a response to the antigens should be visible within a few hours to a few days. Longer reaction times, or the absence of a reaction, suggest poorer immune function. Fifty percent of caregivers were categorized as totally or relatively anergic compared to only 12% of noncaregivers; these immunological deficits were shown in comparison not only to controls but also age-based norms (McCann, 1991).

Caregiver studies have explored psychological concomitants of downward change in immune function by identifying individuals who show immunological change over a period of time. In one such study, approximately 32% of caregivers were classified in an “at risk” category because of downward change on two out of three functional immune measures over 1 year compared to only 14% of noncaregivers (Kiecolt-Glaser et al., 1991). At the initial assessment, these “at risk” caregivers had reported more distress in response to dementia-related patient behaviors and less social support than caregivers who had not shown such uniform declines. Although these two caregiver groups did not differ in amount of time per day they provided care, the total length of time they had provided care, or the extent of the patient’s cognitive impairment, the former were more likely to have institutionalized their spouse between the initial and follow-up assessments.

What do these immunological changes mean for caregivers? Evidence suggests that caregivers show a dampened but stable pattern of immune responses to this chronic stressor; they do not exhibit continued decline (Townsend, Noeker, Deimling, & Bass, 1989). Therefore, immunological status does not simply reflect how long the person has been caregiving but, rather, seems to be affected by the new challenges and struggles caregivers continue to face as part of providing care for their loved one.

Caregiving

Alzheimer’s disease (AD) caregivers are faced with an uncontrollable and unpredictable disease course in which the patient requires ever-increasing amounts of care. While the patient’s survival time after disease onset varies, the modal length is between 5 and 10 years (Hay & Ernst, 1987). Therefore, caregiving has been conceptualized as a chronic stressor. In the studies that follow, caregivers are providing 5 or more hours of care for a family member per week, while controls have no current caregiving responsibilities.

A number of immunological alterations have been related to the stress of caregiving. For example, dementia family caregivers had lower percentages of T lymphocytes and lower T helper/suppressor cell ratios than noncaregivers (Kiecolt-Glaser et al., 1987; Pariente et al., 1997). Other studies suggest that caregivers have fewer NK cells (Castle, Wilkins, Heck, Tanzy, & Fahey, 1995) and T helper cells (Kiecolt-Glaser et al., 1987) compared to noncaregivers. Levels of antibody to Epstein–Barr virus (EBV) virus capsid antigen (VCA) immunoglobulin G (IgG) were higher among 34 family caregivers than 34 matched noncaregivers (Kiecolt-Glaser et al., 1987). Normally, after an active herpesvirus infection, the virus is repressed in a latent state within specific host cells. Immunosuppressed individuals may show elevated levels of antibody to herpesviruses. Higher antibody levels to a latent herpesvirus, including EBV, suggest poorer cellular immune control over viral latency; for example, patients on immunosuppressive therapies often have elevated herpesvirus antibody levels (Glaser & Jones, 1994). In a longitudinal study with 69 spousal caregivers and 69 matched noncaregivers, caregivers showed greater increases in their antibody levels to EBV VCA between intake and the 1-year follow-up compared to controls (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). At the second assessment, the former also had lower lymphocyte proliferative responses to two mitogens, Con A and PHA, than the latter.

Modulation of another latent herpesvirus, herpes simplex virus Type 1 (HSV-1), decreases in the number of circulating B cells, T cells, T helper cells, and T suppressor/cytotoxic cells (Herbert & Cohen, 1993b). On functional assays, stress was associated with a decreased proliferative response to Con A and PHA, as well as lower NK cell activity.

The elderly are likely to be at higher risk than younger individuals following stress-related immunological changes because aging itself weakens the immune system. Qualitative immunological assays show the strongest age-related immune alterations. For example, lymphocyte proliferative responses to PHA, Con A, and pokeweed mitogen decline with age (Maes et al., 1989). In addition, although NK-cell cytotoxicity does not appear to reliably diminish with age, lymphokine-activated NK-cell killing is lower in older populations (Kutza, Kaye, & Murasko, 1995).

As a consequence of these age-related changes, stressful experiences for older adults may have particularly important immunological consequences. If both stress and age can independently weaken the immune system, the interaction of these factors may produce even greater decline. A number of studies have examined these relationships in more detail, particularly studies addressing the physical and psychological effect of one long-term stressor, caregiving for a family member with a progressive dementia.

Bereavement

The loss of a spouse often leads to a stressful and difficult adjustment period. Work examining this experience has suggested that immune function may decline soon after bereavement. For example, compared to prebereavement levels, husbands of cancer patients exhibited significantly lower proliferative response to PHA, Con A, and pokeweed mitogen stimulation 2-months postbereavement; however, 4 to 14 months postbereavement, immune function had improved somewhat (Schleifer, Keller, Camerino, Thornton, & Stein, 1983).

Bereavement studies that included depressed and nondepressed widows have examined the effects of both syndromal depression and stress on immune function. For example, depressed widows showed larger decreases in NK cell activity and poorer
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As discussed earlier, distress-related declines in immune function are larger among the elderly compared to younger individuals (Herbert & Cohen, 1993a). A meta-analysis of the depression and immune function literature found stronger effect sizes for older versus younger subjects on both enumerative and qualitative assays (Herbert & Cohen, 1993a). The combination of distress and an aging immune system may produce more significant deficits in the immune system's ability to function effectively.

Mechanisms for age-related changes in immune function are still under investigation. In earlier literature, pathways thought to account for age-related declines in T-cell function involved a decrease in thymic function or production of thymic hormone (Thompson et al., 1984). These declines would impair the maturation of helper/inducer T lymphocytes, thereby inhibiting their ability to proliferate rapidly in response to antigen. In contrast, more recent work has highlighted the effects of aging on T-cell function. As individuals grow older, there are decreases in the number of cytotoxic effector cells, T-cell proliferation after mitogen stimulation, T-cell responses to new antigens, and T-cell stimulation of B-cell proliferation and maturation (Miller, 1996). These age-related declines may result from alterations in the signal transduction pathways, specifically, defects in calcium mobilization and protein phosphorylation.

Declines in immune function have been linked to increased morbidity and mortality. In fact, these downward changes may actually serve as general markers of physiological aging (Murasco, Weiner, & Kaye, 1988). For example, older adults whose lymphocytes did not proliferate in response to three mitogens were twice as likely to die over a 2-year period as their counterparts who demonstrated a more robust response. Similarly, a study of older adults showed that poorer cell-mediated immunity was linked with greater morbidity and mortality (Wayne, Rhyne, Garby, & Goodwin, 1990). In another longitudinal study examining the 3-year period prior to death, decreases in the absolute number of peripheral blood lymphocytes were associated with mortality (Bender, Nagel, Adler, & Andres, 1986). In addition to marking more general physical decline, these alterations in immune function place individuals at greater risk for immunologically-mediated diseases.

HEALTH IMPLICATIONS

Early investigations showing distress-related declines in immune function were unclear about the significance of such changes on overall physical health. Because down-regulation of immune function does not necessarily indicate poorer health status among...
young and healthy adults, small immunological decrements do not provide clear information on health risks. To assess these effects, responses of chronically stressed populations, such as caregivers, have been compared to nonstressed controls on indices including vaccine response, length of wound healing time, and recovery from surgery.

To determine whether chronic stress was associated with impaired immune responses to influenza virus inoculation, 32 caregivers and 32 well-matched noncaregivers received a vaccine (Kiecolt-Glaser et al., 1996). The timing and strength of antibody and T-cell or cytokine response following vaccination provide data on the body’s response to challenge by pathogens. Although participants in this study had similar vaccine histories, rates of chronic illnesses, and medication usage, caregivers had poorer cellular and humoral immune responses to influenza vaccine than controls. Four weeks after vaccination, caregivers were less likely to show a significant increase in antibody to the vaccine; they had lower levels of interleukin-1β production (IL-1β), an important promoter of immunological activities including antibody responses, and their peripheral blood lymphocytes produced lower levels of IL-2 in response to vaccine stimulation than controls. The immune system must utilize the protective element of vaccines for them to be effective; these data suggest that chronically stressed subjects show deficits in their immune response after vaccination compared to nonstressed peers.

These vaccination results are particularly relevant for older adults. Influenza and pneumonia together are the fourth leading cause of death among adults over the age of 75 (Yoshikawa, 1983), and mortality from influenza infection is four times higher among those over 60 years of age than those under 40 (Burns, Lum, Seigneuret, Giddings, & Goodwin, 1990). Declines in immune function are thought to be related to this increased morbidity and mortality (Kaufman, Bjorndal, Adams, & Linnemann, 1978). Vaccine response data such as those described here (Kiecolt-Glaser et al., 1996) can provide a window on the body’s response to other pathogens such as viruses or bacteria; individuals who show a delayed or blunted vaccine response could be at greater risk for more severe illness.

Because the immune system plays a central role in wound repair, wound healing may also be affected by distress-related immunological changes (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995). Thirteen female caregivers and 13 female noncaregivers underwent a 3.5 mm punch biopsy wound on the forearm; healing was assessed every few days by photography and response to hydrogen peroxide until the wound healed (healing was defined as no scabbing when covered with peroxide). Caregivers took an average of 48.7 days to heal, compared to only 39.3 days in controls, a 24% difference between groups. The peripheral blood lymphocytes of caregivers also produced significantly less IL-1β messenger RNA (mRNA) in response to lipopolysaccharide stimulation in relation to controls. During wound repair, IL-1β regulates enzymes involved with the reconstruction of damaged connective tissue matrices, and it also stimulates production of other cytokines needed for healing. The group difference in IL-1β production suggests that this may be one mechanism related to differences in wound healing.

Older adults undergo surgical procedures more often than do younger individuals, and age itself has been linked to a greater number of postsurgical complications (Linn, Linn, & Jensen, 1983). In one study, younger and older participants were divided into groups based on their preoperative anxiety. After surgery, the older anxious group had significantly more complications than the other three groups. Postoperative morbidity and mortality are substantially higher among older adults compared to younger individuals (Thomas & Ritchie, 1995); further suppression of immune function by depression or chronic stress may place the elderly at even greater risk (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998).

CONCLUSION

In summary, there are clearly significant immunological declines associated with depression, depressed mood, and stress. Unfortunately, these distress-related effects are magnified in elderly populations because the aging process itself contributes to downward change in immune function. The interaction of distress and aging leaves older adults open to physical health complications. Alterations of immune function have been linked to poorer vaccine response and slower wound healing time, as well as increased mortality and morbidity. These trends reveal greater risks for distressed older adults, who are particularly vulnerable to the consequences of immune decline.

This review highlights several significant issues for practitioners working with older adults. First, the treatment of depression in older adults is critical not only for psychological reasons but also to minimize the potential physical health complications of depression. Second, identifying older adults undergoing a chronic stressor, such as those caregiving for an ill family member, may facilitate a search for additional resources from their family or community. Such individuals need emotional outlets and social support to buffer the effects of these stressful experiences. Finally, evidence on vaccine response among elderly caregivers emphasizes the need for older adults to receive regular influenza vaccinations to protect against infection.

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