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Immune Dysregulation and Chronic Stress Among Older Adults: A Review

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Abstract

Aging is associated with a natural dysregulation in immune functioning which may be amplified when it occurs in the context of chronic stress. Family dementia caregiving provides an excellent model to study the impact of chronic stress on immune functioning among older individuals. Empirical data suggest that the stress of caregiving dysregulate multiple components of innate and adaptive immunity. Elderly caregivers have poorer responses to vaccines, impaired control of latent viruses, exaggerated production of inflammatory mediators, and accelerated cellular aging, compared to noncaregiving older adults. The chronic stress-induced immune dysregulation observed among older caregivers appear to be of sufficient magnitude to impact health. Furthermore, evidence suggests that chronic stress lead to premature aging of the immune system.

Keywords

Chronic Stress; Immune Dysregulation; Aging; Vaccine; Herpesviruses; Interleukin-6; Inflammation; Telomeres; Psychoneuroimmunology

Immune Dysregulation and Chronic Stress Among Older Adults: A Review

Aging is associated with a natural decline in immune functioning. Immunosenescence is observed in many facets of both innate and adaptive immunity. For example, older individuals have a poorer natural killer cell (NK) response to stimulatory cytokines than younger individuals [1]. Aging is also associated with impaired activation and proliferation of T- and B-lymphocytes [2]. Furthermore, the B-lymphocytes of elderly individuals produce less antibody than those of younger individuals [3]. In addition, increased production of certain inflammatory mediators is observed during aging [4]. These immunological changes render older individuals more susceptible to a host of age-related diseases. However, immunosenescence appears to place older individuals at greater risk when combined with accumulating chronic illnesses, repeated infections, or other external factors [5]. Chronic stress may be one of the factors leaving elderly individuals more vulnerable to age-related diseases [6,7].

Family dementia caregiving is an excellent model for studying the impact of chronic stress on immune functioning among older adults. Dementia caregiving is a stressful experience because care recipients often exhibit problem behaviors such as wandering or incontinence, and

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cognitive disturbances such as depression or inability to recognize familiar faces [8]. Furthermore, caregiving can be burdensome; caregivers provide an average of 16.6 hours of care per week, often for many years after the dementia diagnosis [9]. In addition, most dementia caregivers are older adults, spouses or older children of the demented patients [9]. Due to the burdensome and stressful nature of caring for a loved one with dementia, caregivers have a higher prevalence of depression and anxiety disorders than age- and gender-matched noncaregiving controls [10].

Caregiving also appears to pose risks for health. Family dementia caregivers are more likely to develop hypertension and hyperlipidemia [11-13]. Caregivers are also at higher risk for developing cardiovascular disorders, diabetes, and infectious diseases, compared to noncaregiving controls [14-19]. Furthermore, in a 4-year longitudinal study, strained caregivers had a 63% higher risk of mortality than comparable community controls [20]. The chronic stress-induced immune dysregulation that has been associated with caregiving is thought to mediate caregivers' increased risk for diseases and mortality [21].

Functional Immune Measures

Earlier studies have shown that relative to noncaregiving controls, family dementia caregivers have dysregulated cellular immunity. For example, proliferative responses to two mitogens, concanavalin A (Con A) and phytohemagglutinin (PHA), were significantly lower among caregivers than controls [14]. Although resting NK cell cytotoxicity did not differ between caregivers and controls, current and former caregivers had a poorer NK response *in vitro* to recombinant interferon-γ (IFN-γ) and interleukin-2 (IL-2) than noncaregiving participants [22-24]. Furthermore, mRNA expression of growth hormone, an immunoenhancing factor, was lower in B-lymphocytes of caregivers, compared to control participants [25]. Although the clinical relevance of these immune changes are unclear, other studies provide evidence that stress-induced immune dysregulation are large enough to impact health.

Vaccination Response

Influenza and pneumonia are the fourth leading causes of death and lead to frequent hospitalizations among older adults aged 65 and over [26]. The U.S. Centers for Disease Control and Prevention now recommends yearly influenza virus vaccinations for every individual aged 50 and over, to reduce the medical burden associated with these infectious diseases [27]. Unfortunately, older adults tend to have poorer responses to immunization than younger individuals [28]. The induction of both T- and B-cell mediated immune responses is necessary to develop efficient protection from viral infections. Furthermore, the ability to mount and to maintain an adequate antibody response following immunization is critical in older adults since poorer responses to vaccine have been associated with a higher incidence of infectious disease [29].

Several studies suggest that dementia caregivers have poorer responses to vaccines than their noncaregiving agemates. For example, following influenza virus immunization, PBLs from caregivers that were stimulated with a Fluzone vaccine antigen produced less IL-1β and IL-2, compared to noncaregiving controls [30]. These results provide evidence of an impaired cellular immune response to the vaccine. A four-fold antibody rise is the conventional standard for determining a significant response to viral vaccine [31]. Dementia caregivers were less likely to have a four-fold increase in antibody titers after influenza immunization, compared to noncaregiving controls [30]. Six weeks after vaccination, only 38% of caregivers had a four-fold increase, compared with 66% of control subjects. These differences were magnified for the oldest caregivers. Among participants aged 70 and over, only 26.3% of the caregivers had a four-fold antibody increase, compared to 60% of the controls [30]. In contrast, among

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nonelderly caregivers of a relative with multiple sclerosis, no difference in the influenza vaccine responses were observed between caregivers and controls [32].

Self-reported psychological distress among caregivers has also been associated with impaired responses to vaccines. Among spouses and offspring of community-dwelling patients with Alzheimer's disease, those who reported more depression and more perceived stress the day of the vaccination had a smaller antibody response to a tetanus vaccine, compared to less distressed individuals [33]. Furthermore, spousal dementia caregivers who reported more worry, rumination, and intrusive thoughts had a smaller antibody response following influenza virus vaccination than caregivers reporting fewer negative repetitive thoughts [34].

The chronic stress of caregiving appears to influence not only the initial vaccine responses, but also their maintenance over time. Among older adults who received a pneumoccoccal pneumonia vaccine for the first time, no differences in antibody responses were detected between caregivers and control participants at 2 weeks, 1 month, and 3 months post-vaccination. However, at 6 months post-immunization, caregivers had significantly lower antibody titers to the vaccine than former caregivers and noncaregiving controls. While the antibody response of caregivers to the bacterial vaccine had declined at 6 months, it remained stable among control participants [35].

Stress-induced impairments in vaccine responses may persist even after the chronic stress has abated. Even when an average of 29 months had elapsed since the death of the care recipient, former caregivers still displayed impaired vaccine responses, compared to control participants [36]. Former caregivers had poorer influenza-specific T-cell responses to an *in vitro* influenza challenge and were less likely to have a four-fold antibody increase to the vaccine, compared to noncaregiving participants [36]. Former caregivers did not differ from current caregivers in terms of their vaccine responses [36]. The lasting, detrimental impact of caregiving on vaccine responses might reflect a premature aging of the immune system associated with chronic stress.

Stress reduction interventions may buffer the impact of caregiving on vaccine responses. Spousal dementia caregivers who were involved in a stress management intervention received an influenza virus vaccination 2−3 weeks after the beginning of the group therapy. Caregivers who did not participate in the intervention and noncaregiving controls were concurrently vaccinated and followed for 6 weeks to examine their responses to the immunization. Caregivers who participated in the stress management intervention were more likely to have a four-fold antibody increase 6 weeks post-vaccination, compared to the control caregivers who did not receive the intervention. Furthermore, caregivers in the intervention group did not differ from noncaregiving controls in terms of their antibody response to the influenza vaccine [37], suggesting a protective impact of the behavioral intervention on the stress-induced impairment in vaccine responses.

The dysregulated production of cortisol, an immunomodulatory hormone secreted in response to stress, might influence vaccine responses. Spousal dementia caregivers who received an influenza immunization had higher salivary cortisol levels than noncaregiving controls over a 6-month period [32,38]. Importantly, caregivers who secreted more cortisol had the lowest production of influenza-specific IgG antibodies, suggesting a key role for cortisol dysregulation in the link between chronic stress and impaired vaccine responses [32].

The decrements in both the T- and B- cell responses to immunization place older caregivers at higher risk of developing infectious illnesses. Studies in which younger adults were experimentally exposed to cold viruses suggest that psychological distress and chronic stressors directly influence the incidence and severity of infectious illnesses [39,40]. Caregivers' impaired vaccine responses put them at further risk for infectious illnesses [29]. Over a 13-month period, family dementia caregivers reported more days of infectious illness, primarily

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upper respiratory infection, than noncaregiving controls, a finding in accord with their deficit in vaccine responses [14]. This suggests that the chronic stress of caregiving leads to impaired vaccine responses and increased susceptibility to infectious illnesses.

Control of latent viruses

Herpesviruses establish a latent infection after the primary infection. Cellular immune responses play an important role in herpesvirus latency. Reactivation may occur when the host's cellular immunity wanes [41]. During reactivation, the viral proteins elicit the host's cellular and humoral immune response, leading to the formation of virus-specific IgG antibodies [42]. The production of higher titers of virus-specific antibodies reflects reactivation of the latent virus and, presumably, poorer cellular immune system control over the latent virus [42]. Reactivation of latent herpesviruses can be a sensitive marker of stress-induced immune dysregulation [43].

There are 8 human herpesviruses, including herpes simplex virus-1 and -2 (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), roseolovirus, and herpesvirus-8. Reactivation of HSV can lead to the eruption of oro-facial or genital lesions, while shingles reflect VZV reactivation [44]. However, among healthy individuals, not all herpesviruses produce clinical symptoms when reactivated. The clinical implications of latent herpesviruses reactivation are most important among immunosuppressed individuals such as organ transplant recipients or HIV-infected individuals [45,46]. Experimental studies suggest that EBV reactivation elicits overproduction of interleukin-6 (IL-6), a cytokine associated with increased risk of a spectrum of age-related diseases [47].

Aging is associated with decreases in cell-mediated immune responses and poorer control over latent viruses. Older adults produce higher levels of EBV-viral capsid antigen (VCA) IgG antibody than younger individuals [48]. Furthermore, CMV mRNA was detected more frequently in urine of older adults, compared to younger adults [49]. In addition, the prevalence of shingles, a consequence of VZV reactivation, is more frequent among aged individuals [50].

Chronic stress is also associated with impaired control over latent viruses. In cross-sectional investigations, older family dementia caregivers had higher antibody titers to CMV than noncaregiving controls [51]. Caregivers also had higher antibody titers to HSV-1 and poorer HSV-1 specific T-cell responses than controls, suggesting impaired clearance of the herpesvirus-infected cells among older individuals under chronic stress [52]. In a longitudinal study, older adults caring for a spouse with dementia had larger increases in EBV-VCA IgG over a 13-month period, compared to noncaregiving older adults [14]. These results suggest that chronic stress leads to a downregulation of latent viruses' specific T-cell response, as well as herpesviruses reactivation.

Interventions that reduce stress may enhance control over latent viruses. In a randomized controlled trial, older adults were assigned to either relaxation training, social contact with a college student, or no intervention. Older adults who practiced relaxation had decreased antibody titers to HSV-1 up to one month after the end of the intervention, while no such changes were seen among the two control groups [53]. Furthermore, in another randomized control trial, 112 older adults completed either a 16-week Tai Chi intervention or a health education control group. At the end of the intervention period, both groups received a VZV vaccine. Individuals who were assigned to the Tai Chi condition had an increase in VZV-specific cellular immunity, while no changes were observed during the health education intervention. Importantly, the increase in VZV cell-mediated immunity during the Tai Chi intervention was of similar magnitude to that of the vaccine response in the health education control group. Moreover, the combination of the Tai Chi intervention and the vaccine led to

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an even greater increase in VZV-specific cellular immunity [54]. Although these behavioral interventions were not administered to a caregiver population, the results suggest that stress-buffering strategies can lead to an improvement in cellular immune-mediated control of latent viruses.

Wound Healing

Wound healing is an orderly process comprising three overlapping phases. The inflammatory phase, initiated quickly after the traumatic disruption of the tissue, serves to clean the damaged tissue of bacteria and debris, and to recruit cells to begin the repair process. The proliferative phase results in the growth of new capillaries from intact blood vessels, and recruitment of fibroblasts ensuring the formation of the new extracellular matrix. Restoration of tissue structure and function occurs during the remodeling phase, with extracellular matrix maturation. Disruption of any of these phases leads to delays in healing [55].

Animal models of wound healing in aging suggest that although the quality of wound repair is not impaired, the healing process is delayed by 20 to 60% [56]. Similar results have been obtained in humans. For example, older adults aged 50 to 88 years old took longer to heal a standardized oral mucosal wound than younger adults aged 18 to 35 years. The age-induced delays in healing persisted even when confounding factors such as medication use and medical morbidity were controlled [57]. Such slowing of wound repair in aging is associated with an increased risk of infection and medical complications [58].

Self-reported stress has been associated with slower wound repair among older individuals. Elderly men and women with naturally occurring leg ulcers were 4 times more likely to be categorized as slow healers if they reported higher levels of depression and anxiety symptoms, compared to those who reported less distress [59]. In a well-controlled experimental study, women who were caring for a spouse or parent diagnosed with dementia took on average 9 more days or 24% longer to heal a 3.5mm standardized wound created by punch biopsy, compared to demographically indistinguishable control participants [60].

Chronic stress appears to disrupt the inflammatory phase of wound repair. In an experimental wound healing study, dementia caregivers' PBLs produced less IL-1β mRNA in response to stimulation with lipopolysaccharide (LPS) than noncaregiving participants [60]. In subsequent work with older women, higher levels of perceived stress was associated with lower production of IL-1α and IL-8 at the wound site, 24 hours after wounding [61]. Since the first 24 hours following wounding is a critical period during which dysregulation of the repair process leads to subsequent delays in healing [62], these results suggest that chronic stress impairs the inflammatory response crucial to the initial phase of wound repair. Animal studies have shown that this stress-induced slowing in wound healing leads to a greater susceptibility to infection by opportunistic organisms, a process that fuels further delay in wound repair [63]. Similarly, in humans, greater stress prior to surgery is associated with longer hospital stays and a higher likelihood of medical complications [64].

Chronic Stress and Inflammation

Aging has been associated with increased production of the circulating proinflammatory cytokine IL-6 [65]. While inflammation is an adaptive response to acute illness or injury, resulting in clearance of pathogens and wound healing, chronic low-grade inflammation can be detrimental to health. Among older adults, higher serum IL-6 levels are related to the development of frailty and disability [66]. Overproduction of IL-6 is also associated with a number of age-related illnesses, including cardiovascular diseases, arthritis, adult-onset diabetes, osteoporosis, periodontal diseases, and certain cancers [4]. Furthermore, in

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epidemiological studies older adults with the highest IL-6 levels had a 2-fold higher risk of mortality compared to those with the lowest IL-6 levels [67].

Chronic stress exacerbates age-related increases in inflammation. In cross-sectional studies, family dementia caregivers had higher IL-6 levels than elderly women undergoing housing relocation, and healthy age-matched controls [68]. A subsequent study with 116 spousal caregivers replicated the finding that chronically stressed older individuals have higher serum IL-6 levels than less stressed individuals [69]. Moreover, in a 6-year longitudinal study, family dementia caregivers' rate of increase in IL-6 was on average four-fold higher than that of noncaregiving controls [70]. Importantly, this chronic stress-induced age-related increase in IL-6 was evident in current as well as in former caregivers [70]. In epidemiological studies, older individuals in the highest IL-6 quartile (more than 3.19 pg/ml) had a two fold higher risk of mortality than individuals in the lowest IL-6 quartile [67]. Applying this mathematical model to the caregiving data revealed that caregivers would reach this threshold around the age of 75, while control participants would reach this criterion after the age of 90, suggesting an accelerated aging of the immune system associated with chronic stress [70].

Chronically stressed or depressed adults may be primed to display an exaggerated inflammatory response to stress or antigen challenge. Older adults reporting greater depressive symptoms had an amplified secretion of IL-6 up to two weeks after influenza immunization, compared to individuals reporting less depression [71]. In another study, older dementia caregivers had a prolonged elevation in IL-6 up to 4 weeks following the influenza vaccination, whereas no change in IL-6 was observed among noncaregiving control participants [34]. In animal studies, chronic stress also led to an exacerbated inflammatory response to subsequent psychological stressors and antigen challenges [72,73]. Depressed men showed a larger increase in IL-6 in response to a laboratory stressor than nondepressed men [74]. The cross-sensitization between stressors and cytokines observed in these studies suggests that chronic stress might prime the inflammatory response to other stressors.

Two neuroendocrine mechanisms have been proposed to explain the link between chronic stress and inflammation. Glucocorticoids usually regulate the inflammatory response by inhibiting the production of IL-6 and therefore terminating the inflammatory cascade. However, among caregivers of children diagnosed with cancer, dexamethasone, a synthetic glucocorticoid, failed to inhibit IL-6 production from whole blood stimulation by LPS [75]. Similarly, lymphocytes of family dementia caregivers were more resistant to *in vitro* glucocorticoid treatment, compared to control participants [38]. In animal studies, splenocytes of mice experiencing social disruption also had decreased sensitivity to the antiproliferative effects of glucocorticoids and produced more IL-6 [76]. Continued exposure to cortisol presumably induces downregulated expression of glucocorticoid receptors, leading to insensitivity to the usual effects of cortisol. This suggests that the insensitivity of immune cells to the inhibitory action of glucocorticoids may promote a state of chronic low-grade inflammation.

Stress-induced norepinephrine secretion elicits gene expression of inflammatory proteins. In an experimental study, the increase in norepinephrine following exposure to a standardized laboratory stressor, the Trier Social Stress Test, activated the nuclear factor NF-κB in peripheral blood monocyte cells (PBMCs) [77]. NF-κB is a transcription factor that influences the expression of the genes of several inflammatory mediators [78]. Therefore, NF-κB may be a mechanism by which psychosocial stress is converted into chronic immune activation. In one study, Alzheimer's caregivers had higher secretion of norepinephrine following a laboratory stressor than controls [79], suggesting that the increased NF-κB activation might explain caregivers' overproduction of IL-6.

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Telomeres and Cellular Aging

Telomeres are specialized nucleoprotein complexes that cap chromosomal ends to ensure chromosomal stability and regulation of the cellular replicative lifespan [80]. Each cellular replication leads to telomere shortening because of the inability of the DNA polymerase to complete the replication of the ends of the linear molecules. Telomerase is an enzyme that partially “rebuilds” telomeres after cell division, but its level is insufficient to maintain chromosomal integrity. When the reduction in telomere length reaches a certain threshold, the cell enters senescence. Normal aging is associated with telomere shortening [80]. Telomere length therefore represents one indicator of a cell's replicating potential and a marker of the biological age of the cell, as opposed to its chronological age [80].

Chronic stress appears to shorten telomere length. In a sample of mothers of chronically ill children and control participants, those who experienced greater perceived stress had shorter telomere length than those who reported lower levels of stress. Among caregivers, the number of years since the beginning of caregiving was associated with shorter telomere length, lower telomerase activity, and greater oxidative stress [81]. In a sample of older adults, dementia caregivers had shorter telomeres in PBMCs and T-cells, compared to age- and gender- matched noncaregiving controls. The basal telemorase activity was higher in caregivers than controls, presumably reflecting an unsuccessful attempt of the cells to compensate for the exaggerated telomere loss [82]. These results provide strong evidence that chronic stress can accelerate biological aging of the immune system.

Conclusion

The chronic stress of caregiving for a loved one with dementia is associated with immune dysregulation. Table 1 provides a summary of the reviewed immune changes associated with caregiving among older adults. The immune dysregulation associated with chronic stress resembles the immunosenescence observed in normal aging. Moreover, an interaction between age and chronic stress is observed for several immune outcomes. For example, older caregivers were less likely to have a four-fold antibody increase to influenza vaccination than younger caregivers. Furthermore, the exacerbated age-related dysregulation in immune functioning persists even after the chronic stress has subsided. Former caregivers exhibited lower NK cell response to IFN-γ and IL-2, poorer response to vaccine, and greater age-related increases in IL-6, even more than 2 years after caregiving ended. In fact, chronic stress may lead to a premature aging of the immune system as evidenced by accelerated telomere shortening in immune cells.

As immune dysregulation associated with caregiving has been firmly established, additional studies are needed to better delineate the neuroendocrine mechanism linking chronic stress and immunity. The glucocorticoid cascade hypothesis and the norepinephrine-induced activation of NF-κB are promising avenues [77,83]. In addition, further studies are needed to investigate resiliency factors that could buffer the detrimental impact of chronic stress on health. Some behavioral interventions, such as relaxation or Tai Chi may attenuate the stress-induced immune dysregulation. Furthermore, some nutritional interventions have promising anti-inflammatory properties, and may even alter inflammatory responses to stress [84,85]. However, it is still unclear if the magnitude of the effect of those interventions is sufficient to attenuate the medical burden associated with caregiving in old age.

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Table 1

Immune Dysregulation Among Older Dementia Caregivers

Immune function	Impact of Chronic Stress	Reference
Functional Measure of Immunity	-Lower blastogenic response to PHA and Con A;	14
	-Lower NK cell response to IFN-γ and IL-2;	22,23
	-Lower Expression of GH mRNA in B-lymphocytes.	25
Responses to Vaccine	-Fewer four-fold antibody increase to viral and bacterial vaccines;	30
	-Lower production of IL-1β and IL-2 from influenza-stimulated PBLs;	30
	-Impaired maintenance of the antibody response over time	35
Control of Latent	-Higher EBV-, CMV-, HSV-1 antibody titers;	14,51,52
Viruses	-Poorer HSV-1 specific T cell response.	52
Wound Healing	-Slower healing of a standardized wound.	60
	-Lower production of IL-1β from stimulated PBLs	60
Inflammation	-Age-related increase in IL-6 production.	70
	-Priming of the inflammatory response to stress	34
Telomeres	-Shorter Telomere Length in PBLs and T-cells.	82