IMMUNE DYSFUNCTION IN THE ELDERLY: THE ROLE OF NUTRITION

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ABSTRACT

Elderly people experience significantly greater morbidity and mortality from infectious diseases than the general population. This apparent susceptibility to infection in the elderly has been attributed to a decline of immune function with age, termed "immune senescence." The main age-associated immune alterations can be listed as follows: (i) Thymic involution resulting in the decreased number of lymphoid precursor T cells. (ii) Reduced proliferative capacity of T cells to antigenic or mitogenic challenges. (iii) Qualitative deficiency of B cells with a reduced response to exogenous antigens. (iv) Alterations in the production and secretion of various cytokines. (v) Compromised activity of the accessory cells, both directly by depressing the chemotactic and phagocytic responses, and indirectly by increasing the prostaglandin production that inhibit the proliferation of T cells. (vi) Other factors like the general physiological conditions, the nutritional state, psychological habit and various hormone levels. The elderly are particularly susceptible to undernutrition that can be caused by a variety of factors including physiologic and psychologic that affect the desire to eat and pose physical or economic barriers that challenge healthy eating behavior. Clinical trials of nutritional supplementation have achieved varied outcomes. Mulitvitamin/mineral supplementation enhanced in vitro immune responses in most trials and clinical benefit in a few studies.

Keywords: Immune function, Aging, Nutrition

INTRODUCTION

Aging is associated with a decline in a large number of physiological functions, including the immune function. Deterioration of immune response is designated immunosenescence and is found in both long- and short-living species as a function of their age relative to life expectancy rather than chronological time (reviewed in 1-3). There is increasing evidence that immunosenescence contributes to morbidity and mortality in human because of the greater incidence of infection. In fact, many studies have suggested a correlation between immune function and age-related risk of morbidity and mortality (4). Clinical observations indicate that elderly people are prone to severe, often lethal, infectious diseases induced by novel pathogens. Infections of respiratory and urinary tracts, endocarditis, septicemia and tuberculosis are commonly encountered in the elderly; moreover, atypical clinical presentations, slow response to treatment and high mortality are all markers of infection in elderly subjects (5). Clinical evidence indicates that with advancing age, immune responses against recall antigens may still be conserved, but the ability to mount primary immune responses against novel antigens declines significantly (6). The impaired ability to mount immune responses to new antigens may result in a high susceptibility to infectious diseases and may limit the efficacy of vaccination strategies in elderly people. Although a number of factors contribute to the increase in infectious diseases in the elderly, this review briefly focuses on immunologic changes that occur with aging. In addition, the role of nutrition in maintaining host defenses in the elderly will be discussed.

AGING IMMUNE SYSTEM
The Role of Thymus in Immunosenescence

For many years, medical science has been aware of the thymus involution associated with aging (reviewed in 7-9). Once the essential role of the thymus in immune development became clear, thymic involution was logically viewed as a clue to the immune dysfunction that accompanied old age. Indeed, the levels of thymic hormones decline after puberty, but they do not differ significantly between elderly and middle-aged subjects (10). Administration of thymic hormones or grafting of thymic tissue can reverse some of the immune deficits associated with aging (11-13). Thymic involution alone, however, is not entirely responsible for immune senescence. It has been shown that lymphocyte maturity is not only a function of the thymus, but also of the type of T cell progenitors that enter the thymus and mature there (14-16). In mice it has been shown that bone marrow progenitor cells that settle in the thymus initiate a coordinated series of interactions with thymic cells that are crucial to normal T cell maturation. Progenitor cells from older mice failed to initiate this interaction (14,15). Outside the thymus, T cells in the bone marrow may demonstrate augmented responses to mitogens (17), and gut-associated lymphoid tissue does not show the decline in T cell cytokine production and receptor expression associated with aging (18,19). These immunologic sites in the body may provide windows to explore the immune dysregulation of aging in greater detail. They may also provide avenues to circumvent the immunodeficiency of aging.

Age-related changes in lymphocyte populations

The number of circulating lymphocytes is similar in aged and younger subjects (reviewed in 20,21). The number of B cells changes little in humans (22-24). There are slightly more CD5+ than CD5- B cells in elderly mice (CD5+ cells are a subpopulation associated with autoantibody production) (25). In contrast, the changes in T cell and natural killer (NK) cell subtypes in the elderly are quite dramatic. The number of mature effector (CD8+) T cells declines with age (26-28). While helper (CD4+) T cells show little change in absolute number, there is also a shift from naive T-cell subpopulations to those associated with activated or memory T cells in mouse and human studies (29,30). This shift may be an important determinant of subsequent cytokine production (31,32). Since lymphocyte subpopulations may also shift in response to coexistent illness (33) some of the published data on lymphocyte subsets in the aged may be confounded by these comorbidities.

One longitudinal study was attempted to determine changes specifically due to aging rather than to comorbid conditions. Virtually no differences in the number of circulating CD3+ or CD4+ T cells were found except for only a slight decline in CD8+ T cells (34). However, this study indicated a marked elevation in the number of circulating NK cells.

Age-related changes in lymphocytes function

The most prominent change in immune function associated with aging is the change in the proliferative response of lymphocyte to antigenic and mitogenic stimuli. Lymphocyte proliferative responses gradually decline throughout life. Lymphocyte proliferative responses from elderly mice and humans are impaired when compared with their younger counterparts(1-3,20,21). Paradoxically, lymphocyte responses were decreased in all but the "oldest" elderly population (i.e., >90 yrs), possibly reflecting a strong survivor bias that may be linked to specific genotypes (35,36). There are several possible explanations for the decrease in proliferative responses. There is a well-documented decline in expression of interleukin-2 (IL-2) (reviewed in 37) and IL-2 receptors (IL-2R) in lymphocytes obtained from elderly mice and humans (1-3). Reduced IL-2R expression may reflect impaired signal processing in aged lymphocytes, which results in a decrease activation of key phosphorylation enzymes, poor mobilization of Ca++, or changes in the lymphocyte membrane (reviewed in 38). Table 1 summarizes the age-related alterations in the immune function. Changes in membranes of lymphocytes appear to affect immune function. The viscosity of T cell membranes is altered in the elderly, whereas the viscosity of B cell membranes is unchanged (39,40). The lipid composition of lymphocyte membranes from elderly subjects shows increased proportions of cholesterol and phospholipids versus that of younger individuals (41). Incubation of lymphocytes obtained from elderly individuals with phosphatidylcholine could restore lymphocyte responses in vitro (42), and the influence of the lipid environment has also been demonstrated in vivo. Alterations in lymphocyte-membrane viscosity may affect cytokine access to membrane-bound receptors (43). Serum from elderly humans is high in very low density lipoproteins (VLDL) and low density lipoproteins (LDL). When added to lymphocyte cultures, sera obtained from the elderly could inhibit IL-2-dependent proliferation of T cells (44).

Lymphocyte responses are regulated by intracellular messenger molecules known as cytokines. Helper T cell responses are divided into 2 types, Th-1 and Th-2. These helper cell functions can be differentiated by the type of cytokines involved. Th-1 responses are driven by IL-2, interferon-gamma (IFN-gamma), and IL-12, but inhibited by IL-4 and IL-10. They favor the expansion of CD8+ effector T cell population and the activation of macrophages. Antibody responses are generally driven by Th-2 cytokines, primarily IL-4 and IL-10. Changes in cytokine production may compromise cell mediated immunity (CMI) in the elderly (2,3,20,21). IL-12 secretion is impaired in elderly mice infected with Mycobacterium tuberculosis, an agent typically controlled by Th-1 responses (45). Helper T cells from elderly mice express high levels of CD44 (CD4+CD44hi) (2,3). These cells produce increased levels of IL-4 and IL-10 (2,3,20,21), which may inhibit the Th-1 cascade. Indeed, IL-10 responses of lymphocytes from elderly mice are exaggerated (3,21). This cytokine profile generally favors the production of antibodies, rather than cellular immunity. In this regard, enhanced IL-10 secretion from non-T cell sources has been linked to autoantibodies (46), a common finding in the elderly. IFN-gamma secretion from aged lymphocytes may also be increased (2,3,20,21). IL-6, another cytokine with broad functions, is elevated in the elderly and may play a role in immune senescence, autoimmunity, tumorigenesis and/or osteoporosis (47,48). However, immune senescence is not merely a shift in the balance from Th-1 to Th-2 responses. It is the overall balance of different cytokines that likely determine the predominant type of immune response in vivo.

Immune Dysfunction in the Elderly

Table 1. Age-Related Changes in the Immune System

Immune Parameters	Changes with age
T cell Subsets:	
* CD3 number	Decrease, No change
* CD4 (helper) number	Decrease, No change
* CD8 (cytotoxic) number	Increase, Decrease
* CD4/CD ratio	Increase, Decrease, No change
* CD44/Pgp-1 (memory) number	Increase
* CD45RA (naive) number	Decrease
T cell Function:	
* T cell antigen response	Decrease
* T cell mitogen response	Decrease
* IL-2 production	Decrease
* Response to IL-2	Decrease
* IL-3, GM-CSF production	Decrease
* IL-4, IL-4, IL-5 production	Increase
* IFN-γ production	Increase. Decrease, No change
B cell Function:	
* B cell number	No change
* B cell mitogen response	Decrease, No change
* Antibody production	Decrease, No change
* Autoantibody production	Increase
Monocyte / Macrophage:	
* Number	No change
* Phgocytosis	No change
* Antigen presentation	Decrease, No change
* IL-1, IL-6, IL-8, TNF-α production	Decrease, Increase, No change
* PGE2 production	No change
* Reactive oxygen radicals	Decrease, Increase, No change
NK cells:	
* Number	No change
* Activity	No change
LAK cells:	
* Activity / number	Decrease, No change
Signal Transduction:	
* Calcium signal generation	Decrease
* Calcium influx and efflux	Decrease
* Inositol phosphate metabolism	Decrease, No change
* Protein tyrosine phosphorylation	Decrease
* MEK / MAPK	Decrease
* Ras Activation	Decrease

ROLE OF NUTRITION IN IMMUNE
FUNCTION OF THE ELDERLY

The elderly are particularly susceptible to undernutrition. Undernutrition can be caused by a variety of factors including physiologic and psychologic. This may affect the desire to eat and pose physical or economic barriers that challenge healthy eating behavior. Undernutrition is typically due to decreased absorptive capacity or insufficient intake of nutrient-rich foods. In addition, other factors, such as comorbidity and polypharmacy, may affect nutritional adequacy. Undernutrition in the elderly is higher among the oldest, the institutionalized, some ethnic minorities, and those of lower socioeconomic status (49-53). It may affect up to 30% of otherwise "healthy elderly (54). Undernourished elders are more likely than their well-nourished counterparts to die from infectious diseases (55) or to develop pressure sores and poor wound healing during acute hospital stays or in long-term institutional facilities (56-58). Even modest systemic nutritional deficiency results in a decline of delayed-type hypersensitivity (DTH) responses and a decreased number of total and mature T cells. Neutrophil function is reduced, and while phagocytosis is generally not affected, the ability to destroy ingested bacteria appears to decline (59). Overnutrition, assessed as obesity, affects immune competence. Obesity has been shown to be a risk factor for infection and poor wound healing (60) and may specifically impair cell-mediated immunity and phagocytic function.

Animal studies have shown that caloric restriction increases longevity (reviewed in 61). The effects of dietary restriction on aging appear to be caloric-specific; alterations in types of fat, protein, and carbohydrates, or supplementation with vitamins and minerals, appear to have no effect on longevity (62). Of the many hypotheses that have been generated to explain this phenomenon, one involves the curtailment of age-related immune senescence. Caloric restriction appears to delay the age-related changes such as the decline in T cell responses (reviewed in 63,64) and the increase of autoimmune responses (65,66). The clinical significance of caloric restriction on longevity is unknown in humans because of the difficulty in

implementing caloric restriction and the uncertainty about how much restriction is beneficial and at what stage of life caloric restriction is tolerable (61). Severe caloric restriction, often classified as protein-calorie malnutrition, has detrimental effects on immune function. Clinical observations have shown atrophy of lymphoid tissue, especially the spleen and thymus, in severe protein-calorie malnutrition. Cell-mediated immunity is more profoundly affected by protein-calorie malnutrition than other limbs of the immune system, but neutrophil function and complement production may also be impaired (59). Inadequate consumption of protein and amino acids affects immune status. Protein deficiency is associated with impaired cellular immune quantity and function and with decreased antibody response (67). Deficiencies of the amino acids arginine and glutamine result in immune changes similar to those seen in the elderly. Arginine has been shown to affect T cell function, wound healing, tumor growth in rats, and the secretion of immunostimulatory hormones such as prolactin, insulin, growth hormone, and insulin-like growth factor (68). Glutamine, a semi-essential amino acid that serves as a fuel source for stimulated lymphocytes and macrophages, enhances T cell, neutrophil, and macrophage function (68,69).

Much attention has been focussed on the impact of lipid consumption on chronic disease, and immune function is affected by lipid status. Linoleic acid, an omega-6 fatty acid, suppresses immune function and is associated with atrophy of lymphoid tissue. Linoleic acid deficiency depresses antibody responses, while excess intake results in diminished T cell function. Intakes of $<=4\%$ of total calories is associated with tumorigenesis, while immunosuppression has been shown to occur at levels $>=15\%$ of total calories (69). Consumption of a low-fat diet high in omega-3 fatty acids may have detrimental effects on immune function. One study reported a decline in the percentage of helper T cells, production of cytokines, and reduced DTH skin response in 22 healthy adults (age $>=40$ years) consuming a diet high in fish versus a diet low in fish (70). There appears to be a positive correlation between dietary fat, especially animal fat, and non-Hodgkin's lymphoma (71). The authors concluded

that this relationship might be due to impaired lymphocyte membrane phospholipid composition, previously shown to affect immune surveillance (72).

Most micronutrients have an upper and lower threshold for optimal immune function (73). Vitamins that play a substantial role in immunity in the elderly include vitamins A, C, D, E, B6, and B12. Minerals that affect immune function include zinc and iron. (Copper and selenium have documented effects on immunity, but deficiencies of these nutrients are rare in humans). The effects of nutritional supplementation on age-related immune alterations are summarized in Table 2. Vitamin A plays an important role in nonspecific immunity by maintaining the integrity of mucus-producing cells (68). Vitamin A also enhances T cell function and antibody production and inhibits tumor growth. A major precursor of vitamin A, beta-carotene, also affects immune function by enhancing monocyte quantity, and may contribute to the cytotoxicity of T cells, B cells, monocytes, and macrophages (69). Vitamin C affects immunity by stimulating the function of PMNs, although functional impairment is evident only at extremely low levels (68,69). Vitamin D is a potent inhibitor of Th-1 lymphocyte responses, generally suppressing monocyte-derived IL-12 production and lymphocyte-derived IL-2 and IFN-gamma (87,89). Th-2 cytokines (IL-4 and IL-10) appear to be relatively unaffected by vitamin D. Analogues of vitamin D have even been used for immune suppression in patients with autoimmune disease and those undergoing transplantation (88,89). Vitamin D deficiency is common in the elderly (90), particularly those with minimal sunlight exposure (e.g., institutionalized elderly) and poor dietary intake of fortified dairy products.

Plasma vitamin E concentration is directly related to DTH. Low levels are associated with an increase in the number of infections (91). There is also some evidence for a negative relationship between vitamin E and IL-2 production, which tends to decline with age (92). Vitamin B6 (pyridoxine) is a coenzyme that plays an important role in protein and nucleic acid production (69). Vitamin B6 deficiency results in atrophy of lymphoid tissue and decreased antibody formation and cellular immunity

(93,94). Lymphocyte function is also impaired in pyridoxine deficiency due to impaired nucleic acid synthesis (95). Vitamin B12 (cyanocobalamin) deficiency is more common among the elderly because of decreased parietal cell production of intrinsic factor, which is necessary for vitamin B12 absorption. As many as 7% to 15% of elderly persons may have vitamin B12 deficiency (96,97). Vitamin B12 is necessary for the production of red blood cells and the myelin sheath covering nerve tissue, but it is especially important as a coenzyme in DNA synthesis. One report indicated that immunoglobulin synthesis was impaired in response to pneumococcal polysaccharide among healthy elderly individuals in whom serum vitamin B12 was subclinically low (98). This effect is pertinent for the elderly, a population at high risk for serious infections caused by Streptococcus pneumoniae.

CONCLUDING REMARKS

As described above, immunosenescence is characterized as an age-dependent diminution of the immune function leading to increased risk of infection, tumor development and autoimmune diseases. Changes in T cell function underlie much of the age-related decline in the protective immune response. Manifestation of the immune dysfunction of T cells is preceded by the involution of the thymus, the organ where T cells differentiate and mature, and is reflected at different steps of early as well as distal events of T cell activation. Examples include a decline in lymphoproliferative ability, alteration in the profile of cytokines produced as well as down-regulation of different events of the signal transduction cascade. Additionally, with age, there is a shift among T cells from naive to memory T cells in humans as well as in mice. Similarly, shifts in cytokine profiles, e.g. a decline in IL-2 production, are in agreement with the shift in the T cell subsets since naive T cells from both young and old subjects are more potent in producing IL-2 than their memory counterparts. The decline in the naive cell population is also in accordance with the higher vulnerability of the elderly to infectious agents, which results from their impaired ability to respond to some newly encountered antigens in vivo.

Table 2. Vitamin/Mineral Supplementation Trials and Immune Response in the Elderly Subjects

Nutrient (s)	Trial Period (months)	Immune Parameters	Observed Changes	Ref.
800 mg vitamin E	1	DTH responses IL-2 response PGE-2 production	Increase Increase Decrease	74
60, 200, 800 IU vitamin E	4	DTH responses Mitogen response	Increase Increase	75
50 mg vitamin E, 100 mg vitamin C, 8000 IU vitamin A	1	T cells, CD4+ cells, CD4/CD8 ratio, Mitogen response	Increase	76
500 mg injection of vitamin C	1	DTH responses	Increase	77
400 mg vitamin C	---	IgG, IgM. and C-3 levels	Increase	78
50 mg vitamin B6	2	CD4+ cells Mitogen response	Increase	79
15, 30, and 60 mg beta carotene	3	CD4+ cells NK cells IL-2 R expression	Increase	79
Vitamin/mineral supplement	12	NK cell CD4+ cells	Increase Decrease	80
Vitamin/mineral supplement	12	IL-2 Mitogen response	Increase	81
Vitamin/mineral supplement	12	DTH responses	Increase	82
220 mg zinc sulfate	1	DTH responses T cells Mitogen response	Increase Increase No change	83
100 mg zinc acetate	3	DTH responses Mitogen response	No change No change	84
100 mg zinc acetate	12	DTH responses NK cells activity Mitogen response	 Increase Increase	85
55 mg zinc sulfate	1	DTH responses	Increase	86

Nutritional abnormalities of macro- and micronutrients are common in the elderly and may compound immune senescence. Physicians and other health professionals should be aware of malnutrition in the elderly and the consequences of both overnutrition and undernutrition when assessing the risk of infection and potential vaccine responsiveness in elderly subjects.

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