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Review

# The Immune-Inflammatory Responses in the Elderly

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**ABSTRACT**

Aging is a series of processes that are controlled by a genetic sequence and cause structural and functional changes in the organism that eventually cause it to die. Population aging is a global problem. With the rapid increase in the average life expectancy in the second half of the 20th century in developed countries, geriatric diseases are more common and become a substantial subject of research. The immune system's weakening and consequent deficiencies are among the most well-known adverse effects of aging. The clinical course, laboratory findings, microbiological epidemiology, treatment, and infection management of infections in the elderly are not only more frequent and severe but also have unique characteristics. Several age-related physiological and anatomical changes, malnutrition, epidemiological variables, and greater sensitivity can all be attributed. Also, while aging can be the cause of infection, the infection can also be the cause of aging. Explaining this situation will enable us to effectively combat possible viral epidemics from now on. In this review, the impact of aging on health was explained, as well as the precautions that should be taken to prevent immune system diseases as people age.

**Keywords:** Aging, immune system, immunity, infection, inflammation

Aging is a normal and inevitable process and is defined as a change in anatomical structure and physical function that occurs without any disease.[1] The United Nations' 2020 World Population Aging report highlights that population aging is an ongoing global problem.[2,3]

The majority of age-related studies concentrate on the physiological aspect of aging when defining and categorizing it. Chronologically, aging is accepted as being over 65 years of age. According to the World Health Organization, in the psychogeriatric phase, 65 years and older is old, and 85 years and over is very old. On the other hand, gerontologists divided old age into three categories: young age (defined as 65 to 74 years old), middle-aged (defined as 75 to 84 years old), and advanced age (defined as over 85 years old).[4] In parallel with the advances in medical care around the world, there has been an increase in the elderly population, especially in developed countries.[5]

The elderly population also is increasing in Turkey. Particularly over the past 20 years, this increase has been more rapid. The proportion of people 65 and older in the population climbed from 3.3% in 1950 to 5.5% in 2000 to 7.5 % in 2012. It is estimated that this rate will exceed 10% in 2030 and increase to 20.8% in 2050. The increase in the elderly population by 22.5% in the last five years indicates that elderly care will gain more importance.[6]

Aging is a multivariate heterogeneous process dependent on genetics, epigenetics, and various factors. It, characterized by both physical and physiological fragility, is associated with a decline in innate immunity and adaptation. Immunity has a tendency to alter abnormally as we age.[7-9] These alterations, which take place over time, result in a decline in biological potential and a rise in illness risk.[10] All organs and tissues, including the immune system, undergo changes as we age. Age-related changes have also an impact on immune system

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components as well as physiological systems such as the endocrine, neurological, digestive, cardiovascular, and musculoskeletal systems. These changes, which affect both innate and adaptive immunity, significantly affect the structure and main functions of leukocyte subsets. In addition, this situation is also accompanied by a transition to a permanent proinflammatory process.[11]

Inflammation is defined as the persistent association between aging and inflammation. Inflammation is stated to be a chronic condition in which proinflammatory mediators such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are elevated.[12,13] "Immunosenescence" is the term used to describe changes brought on by aging in both innate and adaptive immune systems.[14] Immunosenescence describes several changes including the decrease of immune response with age and causes changes. These changes include more severe outcomes of bacterial and viral infections, abnormal spikes, dips, and dysregulated immune responses leading to reduced reactions to vaccination.[15] The autoimmune theory of aging was first put forward by Walford. According to this theory, the immune system tends to lose efficiency over time and there is widespread dysfunction as evidenced by autoimmunity.[16] Cell accumulation at different rates in the age-related immune system forms the cause of autoimmune diseases.[17] According to the immunodeficiency idea, as people age, their bodies become less able to defend themselves against diseases, which cause harm to the organism.[18-20]

Aging, which forms the basis of the deregulation theory, is associated with changes in immune parameters. According to many studies, it has been stated that these age-related diseases can be partially explained by the general deregulation of the immune system response.[21,22]

## IMMUNE SYSTEM

The immune system is the system that screens foreign bodies that come into contact with the human body and prevents biological diseases by separating them from healthy cells and tissues.[9] This system also recognizes pathogens and tumor cells and includes various mechanisms that work to destroy them. This is a system that detects and responds to abnormal cells and molecules that occur in the body and works to prevent diseases such as cancer.[22]

It consists of two interrelated systems that together. There is the natural (non-specific) immune system and the acquired (specific) immune system.[23] The first stage of the immune system, the innate immune system, can distinguish organisms from foreign organisms, but cannot distinguish one pathogen from another. Resistance in the innate immune system includes two general defense systems.[23] The first stage emerges as resistance when epithelial tissue, respiratory tract, gastrointestinal tract, and urogenital mucosa are exposed to microorganisms. The second stage is included antiphagocytic, antimicrobial peptides, chemical signals, natural killer cells (NKC), and inflammatory states associated with inflammation.[23,24] The components of this immune response are phagocytes, NKC, complement, and the epithelial tissue barrier. This system has no memory and reacts, in the same way, every time it encounters microorganisms.[25]

Specific (acquired) immunity is a process that lasts the entirety of an organism's lifespan. It distinguishes living organisms from inanimate organisms. It gives specific responses to foreign molecules with different pathogens.[23] In this system, which includes cellular and humoral immune responses, white blood cells called lymphocytes constitute an important part of the specific immune system. Lymphocytes are classified under two headings as T lymphocytes, which play a role in cellular immunity, and B lymphocytes, which play a role in humoral immunity.[23,25] Cellular immunity is a system in which T cells take part in destroying antigen-carrying cells. T helper (Th) lymphocytes strengthen the innate immune response mechanism by activating phagocytes and enable the humoral immune response mechanism to work by activating B lymphocytes.[25] Cytotoxic T lymphocytes are responsible for the destruction of infected cells. Only protein antigens are recognized by and activated by T cells.[25,26] On the other hand, B lymphocytes are implicated in the humoral immune response because they produce antibodies.[23]

In the circulatory system of some organs, antibodies fight against bacteria and chemicals like poisons and stop them from spreading to the tissues. Among the antigens that it detects and recognizes are molecules such as carbohydrates, proteins, lipids, and nucleic acids.[25]

## INFLAMMATION

Inflammation is a protective response that begins as a result of infection or physical injury by microorganisms.[26,27] Acute inflammation is an immediate and usually short-lived response to an

infection or injury. When inflammation continues without resolution, it becomes chronic and the tissue destruction and the healing process become balanced. This balance is delicate and can change in the direction of destruction at any moment.[28,29] While the acute period is seen as a defensive reaction, the chronic period can be defined as an organized reconstruction process.[29] These immune reactions, which occur for protection under normal conditions, can cause damage to the person's own tissues.[9] Immunological responses that are directed against a person's own tissues result in autoimmune disorders. These reactions manifest themselves as hypersensitivity reactions in the form of an excessive response to environmental stimuli.[22,23]

Immune-mediated inflammatory diseases develop as a result of inflammation brought on by cytokines generated by T lymphocytes and other immune system cells.[30] The type and severity of the stimulus that reveals inflammation, the affected tissue's characteristics, and the individual's response vary. Acute inflammation may totally subside in response to this action, mend with connective tissue regeneration, or develop into chronic inflammation.[30,31]

There are complex cellular connections at the basis of the responses elicited in the tissue. Cells coordinated with various connections are against tissue damage and stimulating structures such as cytokines, activators, and mediators; causing reducing, blocking, or inhibitory responses.[32] The structure and persistence of the bacterial, viral, or parasitic microorganism causing the event determine the type and degree of this response.[33] Although previous studies focused on the humoral defense system, which consists of body fluids such as lymph fluid and blood, in tissue defense and repair, studies in the last century show that this response also occurs in the cells that make up the tissue.[32,34] In these studies, it is also stated that these two systems (humoral and cellular) do not play a role in the inflammation mechanism alone, but also take part in the process in systems that communicate with each other and work in coordination.[35]

Inflammation is a host defense mechanism that offers defense against pathogens, stressors, and tissue damage. This mechanism plays an important role in the progression of many chronic diseases such as arthritis, periodontitis, diabetes, liver cirrhosis, schizophrenia, ulcerative colitis, and atherosclerosis.[24,36-40] Cytokines, chemokines, growth factors, and lipid metabolites are key regulators of immune cell function and differentiation. Therefore, the dysregulation of these substances is thought to be associated with various diseases.[41]

Signal transduction elements such as cytokines, nitric oxide (NO), nuclear factor erythroid 2-related factor 2 (Nrf2), and nuclear factor kappa B (NF-κB) play an important role in the inflammatory response.[42,43] Nitric oxide is an important inflammatory factor synthesized by nitric oxide synthases (NOS) together with cytokine-inducible nitric oxide synthase (iNOS). It plays an important role in the pathogenesis of diseases.[44] The activation of the proinflammatory cytokines TNF-α, IL-1, and IL-6 is controlled by iNOS.[45,46] When infectious microorganisms cross the epithelial layer, circulating microorganisms are recognized by macrophages and neutrophils by the Toll-like receptor (TLR) or receptor specific to each microorganism. The activation of these receptors produces a response, and the resulting response prompts the stimulation of cytokines by activating the transcription factor NF-κB.[47,48]

Through a variety of signaling channels, NF-κB stimulates cyclooxygenase (COX-2) and iNOS. Stimulated COX-2 and iNOS generate proinflammatory cytokines and contribute to the start of the inflammatory process.[49]

Chronic inflammation is defined as the long-term host response to inflammatory stimuli. In autoimmune diseases, a chronic inflammatory response typically develops against self-antigens, low virulence microorganisms, and exogenous substances.[24] Response to persistent infections of pathogens, exogenous, which are characteristically difficult to eradicate, is termed a chronic inflammatory state. The main cellular components of chronic inflammatory responses are macrophages.[47] Activated macrophages play a central role in the destruction of harmful agents such as pathogens. Activated macrophages are responsible for most of the tissue damage and chronic inflammation that occurs in contact sensitivity after a type of inflammatory immune response known as delayed hypersensitivity.[48] These macrophages are responsible for the production of increased amounts of lysosomal enzymes, hydrogen peroxide, some reactive nitrogen intermediates, reactive oxygen intermediates, and many cytokines, growth factors, and other inflammatory mediators.[50] Cytokines synthesized by somatic cells, lymphocytes, macrophages, and monocytes function as messenger molecules responsible for intercellular communication. In addition, it can be found in peptide or glycoprotein structure, which is

involved in body defense.[51] These "hormone-like" molecules are involved in the regulation of the immune response and are synthesized by the relevant cells.[50] They have been classified as lymphokines and monokines according to their cellular origins. Lymphokines are cytokines synthesized by T and B cells, whereas monokines are cytokines synthesized by monocytes.[52]

The initial description of cytokine activities came from Tamiya and Zinsser in 1926. They suggested that cytokines are soluble chemicals secreted from leukocytes that have an impact on vessel wall functions.[53] Research on infectious diseases and antigen-dependent immune responses was examined throughout those years, and further information about cytokines was given supplied. Molecular cloning technology has been used to define cytokines since the 1980s.[52,53] Thus, the discovery of many new cytokines has become possible. As a result of ongoing research, more and more information is gained about cytokines and the role of cytokines in the pathology mechanism of diseases can be better understood.[53]

Cytokines are divided into two classes cytokines synthesized by the Th1 subgroup and those synthesized by the Th2 subgroup. TNF-α and interferon-gamma (IFN-γ), interferon-beta (IFN-β), IL-2, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) are those produced by the Th1 subgroup; while IL-3, IL-4, IL-5, IL-10, and IL-13 are those produced by the Th2 subgroup.[54] Th1-derived cytokines are pro-inflammatory. Th2-derived cytokines exhibit anti-inflammatory capabilities, and these produced cytokines play a role in the pathology of malignant, infectious and autoimmune diseases.[55] Th1-derived cells help macrophages phagocytose and destroy germs more effectively while building an infection defense. Th2-derived cells, on the other hand, direct B cells to make immunoglobulin M (IgM) and immunoglobulin G4 (IgG4), and immunoglobulin E (IgE), which do not fix complement.[54,55] It inhibits both acute and chronic inflammation and cellular sensitization reaction and plays a role in increasing the severity of the humoral immune response.[56] There are four basic categories of cytokines: colony-stimulating factors (CSF), interleukins, TNF-α, and interferons.[57] It was stressed in cytokine research from 1979 that many cytokines have several cell origins in addition to a single cell origin, that they are generated from many cells, and that they display a complicated interaction between the cells of the defense mechanism.[53,54] Thus, numerous cytokines produced by leukocytes started to be referred to as "interleukins".[58]

According to their intended functions, cytokines are divided into four types.[59] These types are cytokines that mediate innate immunity, cytokines that regulate inflammation through immunity, cytokines that enable lymphocyte activation, development, and differentiation, and cytokines that stimulate the growth and differentiation of immature leukocytes.[57,58,60]

## AGING AND IMMUNITY

The immune system changes as we age since it is impacted in many different ways. Immune aging is a period when the immune system's functions occur dysregulated. It contributes to the increase in the tendency of the development of infectious diseases, cancer, and autoimmune diseases in the elderly.[61,62] It has become increasingly intriguing to consider how this dysregulated immune system contributes to the emergence of age-related diseases like osteoporosis, diabetes mellitus, atherosclerosis, and Alzheimer's disease.[61,63] Additionally, when the immune system deteriorates with age, diseases like tuberculosis and pneumonia take on more severe and lethal forms, which is due to the decline in immune system function.[64] Meningitis, infectious diarrhea, endocarditis, which is the inflammation of the inner lining of the heart by encountering a pathogen such as a virus or bacteria, septic arthritis, which is the painful and swollen condition of the joint as a result of bacteria entering the joint, and unexplained fever are also commonly seen and more deadly.[7,63,64] On the other hand, infectious diarrhea causes a large loss of fluid and electrolytes and can make elderly people mentally fog.[61,63,64]

The clinical consequences of immune aging are malignancy, infection, and autoimmune diseases. The two most prevalent illnesses among people over 65 and among the top 10 killers are influenza and pneumonia.[65,66] Due to the weakened immune system brought on by aging, nosocomial infections are frequently encountered in older people. In addition to these immunological deficiencies, other elements that contribute to increased infection rates in the elderly can be said.[11,14] These causes include undernutrition, co-occurring illnesses such as chronic obstructive pulmonary disease, diabetes, liver cirrhosis, heart failure, weakened mucosal barriers, decrease in some reflexes and urinary system, and other anatomical changes.[38,67] When the infections seen in elderly individuals are examined in terms of clinical and symptomatic symptoms, it is seen that there are differences compared to young people.[17,18,21]

For instance, about 30% of older people may not get a fever response in cases of severe infection. Elderly people react non-specifically to infections, and unusual symptoms including anorexia, delirium, falling, or general weakness may be seen.[68]

Cancer death and incidence rates are known to rise after age 65 and fall off beyond age 90.[57] The first defense against tumor cells is made with both acquired and innate immune system cells. These findings are supported by the result that patients with primary or acquired immunodeficiency have a higher incidence of malignancy.[17] However, the role of carcinogenesis, which is a complex pathological process, and the role of immune aging in cancer development will perhaps be explained in future years. Age-related increases in mutant cell burden and duration of exposure to carcinogens both enhance the likelihood of getting cancer in older people.[69,70]

It has been established that the body produces more antibodies as it ages. In addition, in a healthy aged person has been determined that 14% of antinuclear antibodies, 28% of antiphospholipid antibodies, and 22% of rheumatoid factors are positive.[70] Although the cause of the increase in the production of these autoantibodies in the aged is unknown, it can be assumed that it happens because of deficiencies in T cell regulation activities and the disruption of apoptotic cell clearance caused by decreased macrophage activity. Thus, it is well known that abnormal laboratory results and clinical follow-up of rheumatological illnesses, which are frequently observed in older people, present challenges, particularly in the treatment of infections.[11,17] Although it is known that balanced and adequate nutrition is one of the basic requirements of healthy aging, malnutrition rates and the incidence of related comorbidities increase significantly with aging.[71] Physical and cognitive functions deteriorate as a result of chronic diseases, which become more prevalent as we age. In this circumstance, there is a natural decrease in the orientation of food and liquids consumption. Polypharmacy, which results from the increased usage of drugs by people with chronic illnesses, has detrimental effects on their health.[61,72] Polypharmacy impairs eating and drinking habits. In this situation, the development of malnutrition is inevitable. However, as a result of the side effects of the drugs used, new diagnoses and the emergence of new treatments put patients in a vicious circle called a prescription cascade.[67,71,73]

Socioeconomic fragility also causes an increase in malnutrition rates in the elderly and negatively affects the outcome of fighting infectious diseases.[74] Studies indicate that vitamins (folate, A, C, D, E, B6, B12) and minerals (zinc, selenium, iron, and copper) are necessary to maintain normal immune functions. But, there are not enough data to show that they increase immune functions.[75,76]

Aging is known to cause a significant decline in basal metabolic rate, which lowers the daily planned calorie intake. In this instance, the elderly who consume fewer calories are also impacted, and their micronutrient and vitamin ratios fall.[77] All of these lead to numerous other physiological processes, including the immune system weakening in the elderly, to advance negatively. A balanced and sufficient intake of vitamins and nutrients from food is crucial for the health of the elderly because, for instance, magnesium is efficient in the function of more than 300 enzymes in the body.[78] With aging, some changes are seen in both peripheral immune system cells and central nervous system cells. Studies have shown that there is an inverse correlation between the number of microglia and the number of stem cells in the dentate gyrus of aged mice.[79] The quality of life for aged people is severely impacted by the rising illness burden, immune system alterations brought on by aging, and inflammation. Additionally, it is anticipated that all nations will face difficulties in the near future in keeping up with rising health care expenditures, which will put a heavy financial strain on the elderly and their families.[80]

In conclusion, the immune system's decline is one of aging's most well-known adverse effects. As a result of this, immunological deficiencies prevent the body from responding swiftly and successfully to new or previously encountered antigens. The effects of aging on the immune system are manifested by the decrease in the functions of B and T cells in the thymus and bone marrow and mature lymphocytes in secondary lymphoid tissues at different levels. Because of this, when confronted with any threat, an aged person's immune system cannot respond as quickly and effectively as in youth. Especially in this period when the elderly population is increasing and the life expectancy is prolonged, it is important to plan the studies of the elderly in terms of defining these changes in the immune system and the underlying molecular events. Intelligent planning can result in advantageous breakthroughs that will increase both the standard of living and lifespan in this generation and the one after it, perhaps by bolstering the immune systems of the elderly. Mechanisms could involve pathogen-induced tissue damage or

inflammation-induced accelerated cellular aging. In most situations, treating the infection in the elderly results in a positive outcome. The immune system of the elderly cannot mount an immunological response as fast as well as the immune system of the young. It is important to define the changes in the immune system, and the underlying molecular events of the changes, and to support the immune system of the elderly, especially during the pandemic period when the elderly are at risk due to coronavirus.

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