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REVIEW

When wrinkles appear on the immune system can it be reversed?

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ABSTRACT. During aging, physiological and physical frailty occur, which is accompanied by a decline in adaptive and innate immunity, termed '*immunosenescence*' characterized by marked changes in the composition, function, and competence of the human immune system. Moreover, the capabilities of the immune system to defend the human body against infections, to detect and destruct malignant or autoreactive cells decline, resulting in an increase in the susceptibility to infection, development of cancer, as well as autoimmune disorders. The study of age-related changes in immune function is an important area of investigation. In this review, the function of the immune system during aging, as well as the different ways to rejuvenate the aging immune system, is explored, as medical intervention, balanced nutrition, and a healthy life style will be discussed.

Key words: immunosenescence, adaptive immunity, innate immunity, rejuvenation

INTRODUCTION

In a context of physiological and physical integrity changes with aging, immune function declines in terms of both adaptive and innate [1] with marked changes in the composition, function, and competence of the human immune system [2], all together termed as "*immunosenescence*" [3]. Functions of the immune system as defense against infections, response against new invaders, and detection and destruction of malignant or autoreactive cells, decline by aging [4]**.** The availability of naive T cells is substantially affected by age-related thymic atrophy, especially naive CD8+ T-cell reservoir, ending up in a status of increased susceptibility to infections and cancer and an increased incidence of autoimmune disorders [4] . In addition a condition of chronic low-grade inflammation occurs [5], leading to an imbalance between the inflammatory and antiinflammatory states due to elevated levels of pro-inflammatory mediators [6] released by effector memory and senescent T cells [7]. Moreover**,** dysregulation of monocytes takes place leading to reduced phagocytosis [5]. **Wagner *et al***. in 2018 stated that severe infections, symptoms tend to be less in the elderly, and fever is absent in 20 to 30 percent [8] . **In 2000 Norman** suggested that there is a decrease in the ability of immune system to mount an inflammatory cytokine response when facing infection, and the signs of infections are not specific [9]. The efficient immune response is created by a complex network of cells and soluble factors grouped into the innate and adaptive parts of the immune system, which are formed by hematopoietic stem cells (HSC) [10]. In the present review, the function of the immune system during aging is explored as well as the different ways of rejuvenating the aging immune system as medical intervention, good nutrition, and a healthy life style.

IMPACT OF AGING ON THE IMMUNE SYSTEM

Hematopoiesis and mechanism of aging

Aging is associated with profound alterations of the hematopoietic system [11] responsible for producing lymphoid and myeloid cells .The lymphoid branch produces B and T cells that orchestrate the adaptive immune response; the myeloid branch orchestrates the innate immune defense to infection through general pathogen surveillance, phagocytosis, and the inflammatory response [12] as shown in *figure 1* [13]. With aging, a decrease in the volume of hematopoietic tissue in the bone marrow occurs [14], and the regenerative capacity of the hematopoietic stem cells (HSCs) declines [15].__Also, production of myeloid and megakaryotic cells increases resulting in impaired immune functions and elevated incidence of hematological malignancies [16]. The DNA damage response (DDR) in cells is involved in the regulation of cell cycle, cell apoptosis, and senescence [17]. A study released by Li and colleague revealed that HSCs are exposed to DDR stress because of their continuous self-renewal

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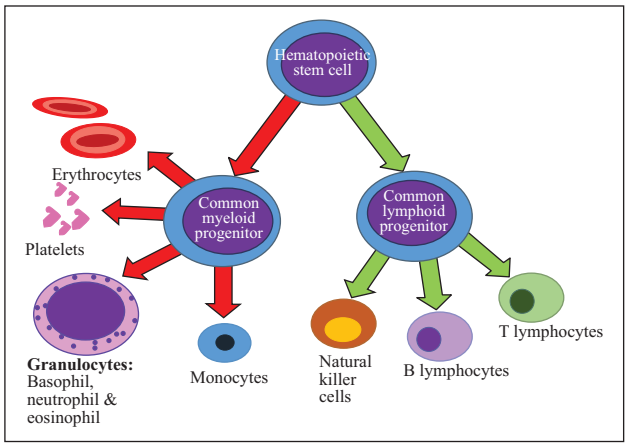

Figure 1
Hematopoiesis from a multipotent stem cell. In the elderly there is skewing toward the myeloid cell differentiation pathway (red arrows) in comparison with the less favored common lymphoid cell differentiation pathway (green arrows); this will result in a decreased production of lymphocytes [13].

process, they proposed that DNA damage may be a principal mechanism that regulates age-dependent stem cell decline [17]. As a consequence of HSC aging a lineage skewing occurs; an upregulation of myeloid-specific genes and a down regulation of lymphoid-specific genes are observed [16]. This skewing toward the myeloid lineage is thought to be due to the decreased number of progenitor cells and colony stimulating factors. Additionally, age-associated changes in the endocrine system lead to reduction in lymphopoiesis, as a result of lowered concentration of growth hormone [18].

Innate immunity

Innate immunity is an unspecific cellular response. Skin and mucous membranes constitute the first line of defense against invaders [19]. The innate immune response is mediated by monocytes, macrophages, neutrophils, dendritic cells, natural killer (NK), and Toll-like receptors [19, 20].

Skin and mucus membrane. By aging the decline of skin cell replacement and epidermal thinning inhibit the barrier function and initiate a pro-inflammatory state [21]. Subcutaneous tissue atrophy [22] and decrease in sweat and sebum production are also observed [23]. In mucous membranes, ciliated cells that remove pathogens, are reduced [24]. Many contributors are involved in skin aging such as alterations in DNA repair and stability, mitochondrial function, cell cycle and apoptosis, proteolysis induced by ubiquitin, cellular metabolism, and hormone decline [25].

Monocytes and Macrophages. The phagocytic activity of monocytes is highly affected and reduced by aging [5]. The ability of cells to produce pro-inflammatory cytokines like TNF-α, IL-1, IL-6, and IL-8 declines [26, 27]**.** Metcalf *et al*. in 2017 observed that cytokine secretion in response to stimulation via TLRs is greatly reduced by aging [28].

Processing and presenting antigens to T cells decline [27], and they become susceptible to the accumulation of reactive oxygen species ROS [29] .These declined functions were attributed to the telomeres shortening of macrophage leading to a decreased GM-CSF but not M-CSF-dependent proliferation of these cells as a result of decreased phosphorylation of STAT5 [29]. In addition, a decline in classical monocytes ($CD14^{+ve}$ $CD16^{-ve}$) and an increase in intermediate ($CD14^{+ve}$ $CD16^{+ve}$) and nonclassical monocytes ($CD14^{+ve}CD16^{++ve}$) were observed by aging [30]. Interestingly, nonclassical monocytes express high levels of miR-146a and exhibit a senescence associated with a secretory phenotype (SASP), and involved in inflammaging [31].

Neutrophils. Aging affects functions of neutrophils in many aspects such as migration route [32], efficiency of phagocytosis [33], and the production of ROS "oxidative burst" [34]. Inaccurate migration was found to be associated with increased constitutive phosphoinositide 3-kinase (PI3K) signaling [35]. PI3K-blocking strategies, specifically inhibition of PI3Kγ or PI3Kδ, restored neutrophil migratory accuracy [35] and might help improve outcomes during infection and reduce inflammation [36]. Neutrophils showed a reduced chemotaxis to the different stimuli [37] and a reduced ability to extrude their DNA as networks of extracellular fibers (NETs) responsible to entrap bacteria extracellularly [34], causing an alteration in pathogen destruction mechanism [38]. In addition, the significant decrease in T-cell-like receptor repertoire diversity (referred to as TCRL) in old age is a mechanism of immunosenescence in neutrophils [39]. Moreover, an age-associated reduction in TLR1 expression on neutrophils was found to be associated with reduced chemokine (IL8) production, reduced rescue from apoptosis, and lower expression of activation markers, resulting from reduced bioenergetics in neutrophils [40], which explains the recurring infections [35], especially of the skin and respiratory tract in seniors [32]. Also, it was reported that the lowered production of ROS due to aging [34] leads ing to a reduced ability to eliminate bacteria and fungi [41].

Dendritic cells. Dendritic cells (DCs) are professional antigen-presenting cells, responsible for the first recognition of pathogens, migration to regional lymph nodes, phagocytosis, priming of naive T cells, and regulation of B and NK cells' response [42]. They are strategically placed between internal and external environment, which enables them to link innate and adaptive immunity [42]. Impaired functions of DCs by aging [43] include defective migration, phagocytosis [44], and signaling pathways [45]. They also exhibit mitochondrial dysfunction, illustrated by reduced ATP turnover and coupling efficiency, decreased baseline oxidative phosphorylation, and greater proton leak and reactive oxygen species (ROS) production [46]. It was observed that DC from older mice have a poor ability to stimulate a CD8+ T cell-mediated cytotoxic response [47], because of the reduced production of TNF-α which is a determining factor in the DC that mediate CD8+ T cell response [48].

Natural Killer cells. The NK cells are key component of innate immunity which are involved in the immune response to influenza infection [49] and vaccine [50]. They are responsible for eliminating virus-infected or tumor cells and in the regulation of the immune response by producing cytokines and chemokines that activate other cellular components of innate and adaptive immunity [51]**.** Changes in NK cell biology that accompany human aging are manifested as an increase in NK cell numbers, due to the increase of $CD56^{dim}$ NK cells [52] and a decrease of CD56bright cells [53], leading to an altered NK cell subset distribution [54] and a decrease of about 75% in the amount of IFN-γ secreted by NK cells [55]. Additionally, the expression of activating NK cell receptors NKp46 and NKp30 declines with age, NK cell cytotoxicity toward cancer cells is reduced with age [52, 54] due to reduced release of perforin [54], increased reactivation rates of latent Mycobacterium tuberculosis [56], CMV seropositivity, and proinflammatory status occur [7] leading to an increased incidence of bacterial and fungal infection [57]. Conversely, aging-related functional NK cell deficiency was completely reversed by injecting soluble IL-15/IL-15Rα complexes [58].

Toll-like receptors. Toll-like receptors (TLRs) are receptors that are distributed in the body [59]. By aging, a down regulation of toll-like receptors (TLRs) is observed, a process that contributes to the lack of effective recognition of invaders [60]. Research studies have implicated specific signaling pathways in alterations in TLR function in the context of human aging. These include decreased PI3-kinase activity in MDDCs (associated with increased PTEN phosphorylation) [45] and an impairment in downregulation of STAT1 phosphorylation in macrophages [61]. Microglia are mononuclear immune cells of the central nervous system (CNS) [62], they express all TLRs but their expression is affected by aging, which is a risk factor of neurodegenerative diseases, such as Alzheimer's disease (AD) [63].

Adaptive immunity

Adaptive immunity is characterized by the generation of highly antigen-specific memory after encountering an antigen [64]. By aging, a reduced B and T cell responses [8] and a decrease in the production of T and B cells occur [65]. As a result the immune system becomes less able to distinguish self-belongings from nonself one [66], and autoimmune disorders become more common [67].

***Thymic involution.*.** One of the most dramatic changes that occur in the aged immune system is the involution of the thymus gland. As a result, a decrease in both stromal and thymocyte cellularity and a loss of tissue organization occur [68], the thymus function decreases [69] and production of naive T cells declines [69] along with the accumulation of memory T cells that contributes to a shift in T-cell population toward memory T-cell dominance (*figure 2*) [68]. Therefore, the ability to respond to new immunological challenges, including vaccines, is compromised, and

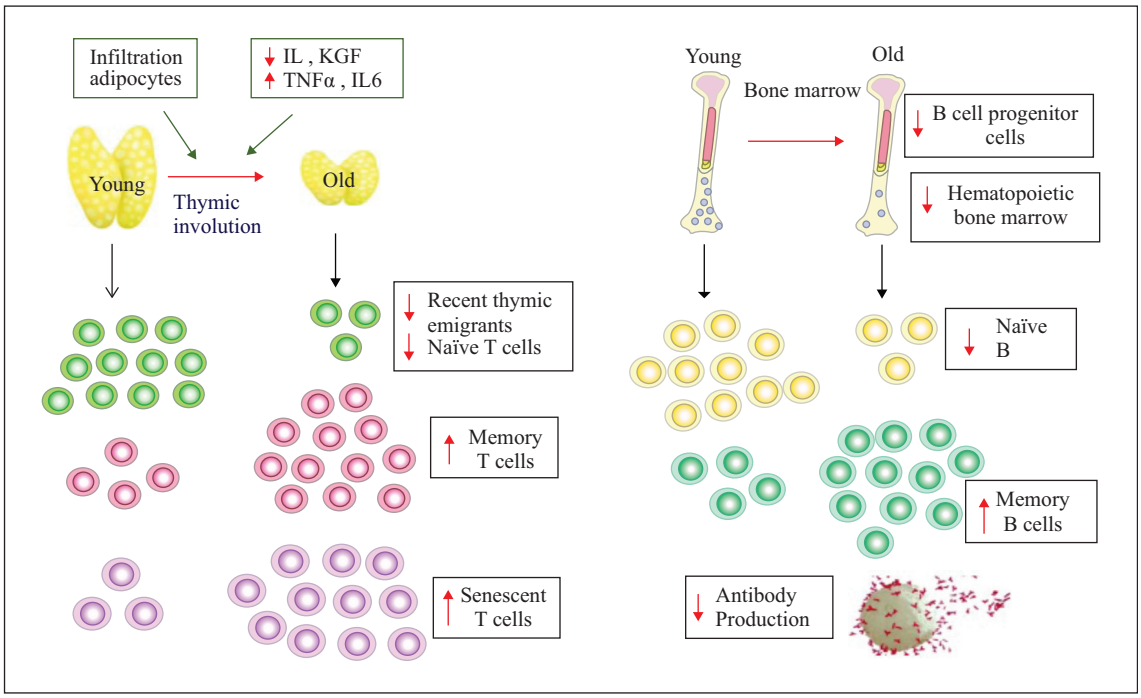

Figure 2

Age-related alterations in adaptive immune cells [68]. The thymus is located in the right upper side of the figure in yellow color as shown in young age it is bigger than that of old (getting smaller with age) the young thymus release a large amount of naive T cells showed as (green circles) small amount of memory T cells shown as (red circles) and very little amount of senescent T cells purple cells arrow to the upper side increase arrow directed to down decrease in the upper left side of the figure in aged individuals the bone marrow produces a very little amount of naive B cells shown in the figure as (yellow circles) a decrease in the antibody production and a large amount of memory B cells shown (turquoise circles).

susceptibility to infection, autoimmune diseases, and cancer increases [70].

T lymphocytes. The hallmarks of T cell immunesenescence include: accumulation of $CD28^{-ve}CD57^{+ve}$ T cells with shortened telomeres and reduced proliferative capacity [71], the lymphocyte potassium channel inhibitory pattern is altered, regulators of calcium influx kinetics contribute to the development of age-related changes of T cell function [72] and a decrease in intracellular calcium levels and alterations in the signal transduction pathways NF kB and MAPK have been observed [73, 74], a reduction of the membrane receptors CD28 (important in lymphocyte activation) and CD27 (limited proliferative capacity by T lymphocytes) [75] occurs. It was found that decreased miR-181a is associated with age, it controls lymphocyte activation via their T cell receptor. This decline results in poor cell activation and also autoantigen recognition [76]. Endogenous p53 isoforms Δ133p53 and p53β are physiological regulators of proliferation and senescence in human T lymphocytes. Conversely, the knockdown of Δ133 and the over expression of p53 β in CD8 + CD28+ cells inhibits cell proliferation and induced senescence [77]. T cells with senescent characteristics increase with age and exhibit constitutive p38 MAPK activation [78], due to the formation of a complex between MAP kinases and the sestrin family of proteins which results in kinase activation [79]. Furthermore, knockdown of sestrins [79] or inhibition of p38 MAP kinase restored T cell proliferative capacity [80].

Naive T cells. Naive T cells are long-lived cells and can circulate for years if they did not encounter the appropriate antigen. In old age they may die before finding their appropriate antigen [81]; therefore, the net outcome of naive T-cell output becomes reduced by aging [70]. Additionally an altered expression of costimulatory and inhibitory receptors occurs [82] causing many functional defects including impaired ability to multiply and become "effector" cells. As a result, the ability of the elderly to mount a successful immune response to new antigens is diminished, their ability to respond to infections increases, vaccine efficacy decreases [83].

Senescent Memory T cells. Memory T cells are generated when encountering an antigen. Upon reexposure to the same antigen, memory T cells recognize it and launch a vigorous response. By time, repeated exposure to antigens increases the number of protective memory T cells [84] memory T cells of seniors are often senescent, and dysfunctional as they lose the ability to proliferate and divide [83]; and secrete high levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha and IL-6 [57, 83]. **Chou and Effros 2013** stated that aging of memory T cells may result from lifetime exposure to common viral infections such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV) [85] that remain inactive in the body for decades, triggering a chronic, low-intensity response from memory cells and other adaptive immune cells and inducing chronic inflammation. There is also an evidence that senescent memory T cells may suppress other types of immune cells [85]; they accumulate in tissues with age, causing degeneration and malignant transformation [86].

Regulatory T cells. Jagger in 2014 revealed that regulatory T cells $CD4^{+ve}CD25^{+ve}Foxp3^{+ve}$ T cells play a pivotal role in maintaining immune homeostasis [87] by suppressing immune responses [88] they accumulate with age and weaken the immune response to pathogens or malignant cells [87]**.** Furthermore, their function may change with age [87, 89] as high suppressive activity could allow a greater risk of cancer, whereas impaired suppressive activity could confer a greater risk of autoimmune diseases. Thus, a balanced functioning of regulatory T cells is necessary to avoid chronic inflammation, maintaining immune protection against infections and cancer [87].

Helper T cells. CD4+ T-helper cells in the context of aging exhibit a Th2 profile (i.e., IL-4 producing cells) dominance over a Th1 profile (i.e., IFN-γ producing cells) [90]. In addition, Th17 cells that are responsible for IL-17 production and are associated with autoimmunity and inflammatory diseases accumulate by aging [91].

Cytotoxic T cells. CD8+ cytotoxic T cells mediate lytic reactivity once activated and can kill infected cells directly by the production of cytotoxins such as perforins and granzymes [92]. The accumulation of late-stage potentially differentiated cytotoxic T cells as a result of the substantial telomere erosion that affects the replicative capacity of $CD8^+$ T cells during aging [93] is often considered a hallmark of immunosenescence [94].

B lymphocytes. Functions of B cells are affected at a mechanistic level. B-cell lymphopoiesis decreases [95]**,** a reduced expression of genes for the differentiation occurs [96] leading to a decline in the frequency of naive B cells ($CD27^{-ve}$ IgD^{+ve}) and an increase in memory B cells [97]. In addition, a reduction in crucial gene products for immunoglobulin class switch occurs which in turn affects the efficacy of humoral immune responses [96]. A decline in CD4 T cell and dendritic cell functioning, along with intrinsic changes in B cells resulting in age-associated reduction in number and size of germinal centers, are all contributing factors toward the decline in antibody production by older individuals with age [98]. One of the major manifestations of B-cell aging is the changes in their antibody repertoire including a shift in antibody production from IgG to IgM, from high affinity to low affinity, and from specificity for foreign antigens to specificity for self- antigens [71, 99]. Duggal *et al.* in 2012 revealed that immunosuppressive $CD19^{+ve}$ $CD24^{hi}$ $CD38^{hi}$ B cells subsets are affected in their number and function which might be a factor contributing toward increased risk of systemic autoimmunity by aging [100].

Antibody diversity. It has been stated that B-cell diversity is collapsed and decreased by aging [101]. The

immune system becomes disabled to mount an effective and specific antibodies production where a nonspecific antibody production prevails, making seniors vulnerable to infections and affecting their general health status [102]. Despite being quantitatively preserved, antibodies show impaired qualitative attachment to antigens, consequently infectious diseases such as pneumonia, influenza, infective endocarditis, and tetanus are more common among the elderly. Also, this explains why vaccines are less effective among them and why they must take booster shots [103].

PHENOTYPICAL AND FUNCTIONAL ALTERATIONS IN ELDERLY (*TABLE 1*)

How can immune system survive aging?

Rejuvenation strategies

Impact of lifestyle modifications on immunesenescence.

Stress Management.
Stress can be managed by meditation, mindfulness, and yoga that can promote positive emotional states [120]. Interestingly, it was found that the mind-body therapies decrease the markers of inflammation and increase the anti-viral-related immune responses and cell-mediated immunity [121], and increase IgA [122]. A recent study revealed that yoga reduces pro-inflammatory markers, as CRP and IL-1beta increases antiinflammatory cytokines such as IL-10 and could mediate inflammation at the genomic level, by changing the levels of proteins that control the DNA transcription of proinflammatory cytokine [123]. Another study found that it also improves the levels of cytotoxic T cells, B lymphocytes, and natural killer cells [124].

Sleep. Unfortunately, deprivation of sleep increases expression of genes responsible for DNA damage [125] and thus increases senescence, along with the enhancement of the proinflammatory profile [125] and a decrease in natural killer cell responses and T-cell cytokine production [125], but regular sleep patterns correlate with better immunological responses [126] and promote the redistribution of antigenic memories initially those held by antigen-presenting cells[127].

Oxytocin (Cuddle hormone). Oxytocin (OT) plays an important role in the functioning of the immune system, because the oxytocin secretory system (OSS) has a pivotal role in the development of thymus and bone marrow, strengthens immune defense, performs immune surveillance, inhibits immune damages, and maintains immune homeostasis. As a result OT inhibits inflammation, exerts antibiotic-like effect, promotes wound healing, and regenerates and suppresses immune disorders associated with stress, the OSS can release OT that act on immune system by activating OT receptors [128].

Sunlight. Sunlight is an important factor that positively impacts immune functioning and reduces the incidence of autoimmune diseases [129] and cancer [130]. Interestingly, it was revealed that sunlight energizes T cells through a separate mechanism from vitamin D production and that low levels of blue light, found in sun rays, make T cells move faster, allowing them to report T cells as either helper or killer and as the first immune cells that respond to sunlight. In addition they proved that T lymphocytes possess intrinsic photosensitivity which may enhance their motility in skin. They showed that blue light triggers the production of H_2O_2 that stimulates signaling pathway enhancing T-cell motility in vitro [131].

Water. Succeeding cold exposure (CE) leads to the increase of leukocytes, granulocytes, circulating levels of IL-6, and NK cells responses by pretreatment with exercise in water (18 °C) and thus acute CE has immune-stimulating effects [132]. **Shevchuk and Radoja** revealed that a daily brief cold stress can increase both numbers and activity of peripheral cytotoxic T-lymphocytes and NK cells, which are the major effectors of adaptive and innate tumor immunity [133].

Fasting. During normal and healthy operation, the immune system detects and removes senescent cells; this operation ceases and fails by aging, leading to the accumulation of senescent cells, which are partially responsible for aging [134]**.** Upon fasting, the immune system tries to save energy, by recycling a lot of the immune cells which are not needed, especially the damaged ones, fasting can help body get back to normal, and possibly even better than before fasting [134]. Another recent study by **Choi *et al*.**,2017 showed that long-term fasting, followed by refeeding, promotes the antiinflammatory effects, decreases the aging biological rate, and reverses a variety of autoimmune disorders as well as immunosenescence by killing old and damaged cells and replacing them with young and functional ones and causes apoptosis of autoreactive T cells, which are replaced by newly generated naive T cells during the refeeding period [135]**,** because it reduces circulating Insulin-like Growth Factor-1 **(**IGF-1) levels and protein kinase A (PKA) activity in various cell populations [136]. Recently, **Rangan *et al*. in 2019** revealed that fasting by water only increased regenerative activity of immune system and reduces inflammatory markers [137]**.**

Calorie restriction. A new study released by **Lee and Longo** stated that caloric restriction program of a 20–40% reduction of food consumption relative to normal intake is very effective in the regulation of aging [138]**.** Many studies revealed that long-term caloric restriction results in reduction of the risk of age-related diseases, including type 2 diabetes mellitus, cardiovascular disease, and cancer [139]**.** Other experimental studies have shown that caloric restriction maintains a youthful function of the thymus gland, reduces immune senescence during aging, increases proliferation and diversity of T cells [140]**,** and improves multiple aspects of immune activity, particularly T-cell function [141], response to mitogens [142], and enhances the activity of both cytotoxic T-lymphocytes [143], NK cells and the ability of mononuclear cells to produce proinflammatory cytokines [142]. Periodic

Table 1
Phenotypical and functional alterations in elderly individuals

Alterations in elderly	Phenotypical	Functional
Skin	Subcutaneous tissue atrophy [22] epidermal thinning ultra-structural changes of the mucus membranes of hair cells [24]	Decreased barrier function, pro-inflammatory state, and gradual deterioration of the epidermal immune response [21]
Peripheral lymphoid tissue	Shrinkage of the volume of the peripheral lymphoid tissue [104]	Decline of absolute and relative concentrations of naive T cells in the blood [104]
Monocytes	1-No change in the number [105] 2- Increase in nonclassical monocytes express high levels of miR-146a and exhibit a senescence associated secretory phenotype (SASP) [31]	Migratory/ chemotaxis,Phagocytic, Cytotoxic abilities were reduced [105]
Dendritic cell	1-Reduced number [105] and lower maturation [48] 2-Reduction in plasmacytoid DCs and unaltered frequency of myeloid DCs [106] decline in $CD141^{+ve}$ DCs, inducer of T helper 1 cell and cytotoxic T lymphocyte responses [107] [108]	1-chemotaxis,Phagocytic,abilities were affected [105] 2-T helper 1 cell responses and cytotoxic T lymphocyte responses were affected [108]
Neutrophils	No change in the number [105]	Migratory/ chemotaxis,Phagocytic, Cytotoxic abilities were reduced [105]
Natural killer cell	Impaired maturation [109] increase in NK cell numbers, due to expansion of $CD56^{dim}$ NK cells [105, 110]	Migratory and chemotaxicity were reduced [105] Impaired function of NK cells [109], slower resolution of inflammatory responses increased incidence of bacterial and fungal infection [57]
Toll like receptor	changes in expression of costimulatory markers CD80 and CD86 on monocytes showed a generalized, highly significant decrease in TLR-induced upregulation of CD80 [111]	Inappropriate persistence of TLR activation lack of effective antigen recognition [112], dysregulation of TLR signaling [112]
Peripheral lymphoid tissue	Shrinkage of the volume of the peripheral lymphoid tissue [104]	Decline of absolute and relative concentrations of naive T cells in the blood [104]
Thymus	Involution of thymus [104] replaced by connective and lipoid tissues[113]	Lower number of naive T- cell and thymic hormone [114]
T- cell	Shortening of the average telomere length of T cells [104] Increase in the Number of memory and effector cells increase in the expanded clones of CD8+ and CD4+ memory T cells (oligoclonal expansion) and regulatory T cells [18] Decrease in the Number of naïve T cells [18]	Lymphocyte decline in their proliferative capacity [115, 116] Increase in the levels of pro- inflammatory cytokines [18] Ability of the elderly to mount a successful immune response to new antigens is diminished [83]
B cell	Decrease in the Expression of costimulatory molecules (CD27, CD40) [18] Decline in the frequency of naïve B cells ($CD27^{-ve}$ IgD^{+ve}) and an increase in memory B cells [97] [118] Decline in the immunosuppressive $CD19^{+ve}$ $CD24^{hi}$ $CD38^{hi}$ B cells [100]	Antibody affinity and specificity as well as diversity, decreases [117] Impaired B cell responses and defective antibody production reflected in a reduced ability to effectively respond against viruses and bacteria [119] Decrease of Isotype switching leading to the risk of autoantibody responses and autoimmunity [18, 100]

dietary restrictions were found to reverse age-dependent immune dysfunction by killing autoimmune cells [144] and could rejuvenate aged HSCs by reduction of the nutrient supply and the clearance of senescent cells [15]. Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation [145].

Mediterranean Diet. The Mediterranean diet is a dietary pattern based on foods and drinks traditionally consumed by people in the region surrounding the Mediterranean Sea [146]. This diet has been shown to protect against several age- and inflammation-related conditions including diabetes, atherosclerosis, obesity, cancers, and neurodegenerative diseases. It is characterized by inclusion of olive oil, fruits, vegetables, legumes, whole grains, nuts, and seeds; with moderate amounts of fish, poultry, cheese, yogurt, and eggs; limited inclusion of red meat, processed food, and foods rich in refined sugars [147]**.** The adoption of the Mediterranean diet by older adults has also been associated with improvement in immune responses, particularly dendritic cell function [148].

Exercise. Reduced physical activity leads to increased adiposity and systemic inflammation [149]. There is a link between aging of immune system and inflammation [150], but regular physical activity has been associated with exert antiinflammatory and anti immunesenescence effects, potentially delaying the health declines [151] lowering the levels of pro-inflammatory cytokines such as IL-6, TNF-α in the elderly [152] and improving neutrophil chemotaxis [153]. Regular exercise has been shown to improve neutrophil microbicidal functions which reduces the risk of infectious disease [151], with increased immune cell telomere length, improved vaccine responses and immune system function [154]. **Takahashi and colleague** revealed that moderate walking reduces basal levels of ROS leading to an improved immune-surveillance in seniors [155]. Exercise and aerobics

are thought to mobilize aged T cells into the blood [156] leading to their degradation, allowing more space for naive T cells [126] and induce changes in immune cell numbers and functions. A clear response of CD4+ T cells, rather than CD8+ T cells or NK cells, was noted [157]. In addition aerobics improved immune response and reduced inflammatory cytokines [6]. Recently, **Duggal *et al***. observed that aged cyclists had higher levels of IL-7, IL-15 which are thymo protective cytokines that maintain naive T cells in the periphery and lower levels of IL-6 which causes thymus involution [158]**.**

Vitamins. Micronutrients are important for natural defenses on three levels:
– To support physical barriers (skin/mucosa): Vitamins A, C, E and the trace element zinc assist in enhancing the skin barrier function [111, 159].
– To support cellular immunity: vitamins A, B6, B12, D,C, E, folic acid and the trace elements zinc, iron work in synergy to support cellular and humoral immune responses [159].
– Antibody production: The vitamins A, B6, B12, D, E and folic acid and the trace elements zinc are essential for antibody production [111, 159].

Vitamin A
By aging skin becomes thinner resulting in a decreased barrier function because of the decrease in the protein transforming growth factor beta that controls many cellular functions. As a result dermal fibroblasts will not be converted into fat cells, and cells will not produce the antimicrobial peptide cathelicidin, which protects against bacterial infections [160]. Vitamin A increases the epidermal thickness by the upregulation of transcription factors, collagen genes responsible for wound healing, improving extracellular matrix microenvironment, extracellular matrix production, and activation of dermal fibroblasts in elderly [161]. Vitamin A deficiency leads to a poor immune response to infection especially trans retinoic acid (RA), which is an active form of the vitamin that ensures immune homeostasis through regulating cell homing and differentiation. During infections and autoimmune disease, it activates and enhances T-cell responses [162] to cancer, infections, intestinal inflammation, and immune-mediated diseases as autoimmune diseases associated with aging [162].

Vitamin B12 and folate
Vitamin B_{12} and folate are associated with preventing chronic diseases associated with aging through the methylation of homocysteine [163]. Elevated homocysteine and lower vitamin B12 levels impact the immune system, causing increased inflammation and antioxidant agents damage that catalyzes physiological aging in all systems [164]. A recent study by **Laird *et al*., (2018)** revealed that adults over 50 are at risk of deficiency in vitamin B12 and folate because their ability to absorb B12 from food decreases; thus, they recommended that B12 must be obtained from supplements and B12-fortified foods like cereals [165]. It is worth noting that most of elderly suffer from megaloblastic anemia, due to vitamin B12 deficiency [166].

Vitamin E
Recently, it was found that aged people have lower levels of vitamin E and magnesium that was found to associate age-related diseases [167]. Many studies recommend daily vitamin E supplementation in the elderly, as it enhances the differentiation of immature T cells in thymus [168], the function of immune cells as neutrophils, T-cells, B-cells, and NK-cells [169], and the age-associated decline in naive T-cell function [170]. Moreover, it was found that vitamin E regulates lipid rafts and membrane fluidity on the surface of immune cells in naive $CD4^+$ T cells of old mice; it also improves age-related early T-cell signaling events in naive helper T cells [171]. As a result, resistance to infection increases [169] and reduces the risk of influenza virus in elderly [168].

Vitamin D
Vitamin D (Vit. D) is an important factor for immune functioning because it stimulates the clearance and phagocytosis of macrophages, and protects immune cells against apoptosis by regulating both extranuclear protein functions and gene expression signaling [172]. Vitamin D intake decreases with age [173], in early life, exposure to the sun activates pre-vitamin D under the skin, by aging, the body composition changes and thus pre-vitamin D is lost. As a result, older people produce less Vit. D even if they get plenty of sunlight [173], where supplementation with Vit. D modulates aging-related systemic inflammation including immunosenescence [174]. In addition it was found that magnesium is essential for vitamin D metabolism. Otherwise vitamin D will remain stored and inactive [175]. Vit. D has also emerged as a key modulator of a range of immune functions including monocyte differentiation into macrophages, less production of pro-inflammatory cytokines by macrophages inhibition of Th1 and Th17 responses, and regulation of B-cell proliferation [176].

Vitamin C
Vitamin C supplementation maintains immune function as we age [177], supports the functions of both the innate and adaptive immune systems, plays an important role in the defense against bacteria and viruses [178], and reduces the duration of common cold [177]. In addition to stimulating immunity, vitamin C also appears to restrain excessive immune activity, perhaps in part by interfering with the synthesis of inflammatory cytokines [178].

Zinc. Zinc is a trace element required for multiple immune cell tasks including suppression of production of pro-inflammatory cytokines (IL1β, TNFα) by monocytes/macrophages and reduction of reactive oxygen species (ROS) [179]. Additionally, it was found that supplementation of Zinc for six months improves antiinflammatory cytokines profile [180]**,** and decreases the markers of inflammation like IL-6 and C-reactive protein [181]**.** Another study on older individuals in nursing homes residents observed that

older individuals with normal zinc levels had lower incidence of both the pneumonia and antibiotic usage compared with zinc-deficient individuals [182]. Zinc supplementation has been shown to reduce infection incidence in older adults [180] and has many effects indicative of reversed immunesenescence including: improved NK cell cytotoxicity [183], modification of Th1/Th2 balance [184], restores the serum thymulin activity [185] and improves vaccine responses [186].

Iron. Mocchegiani *et al*., 2012 revealed that iron is essential for maintaining immune and antioxidant function during aging [187]. In chronic states of inflammation such as obesity or aging, iron status becomes impaired [188] and malnutrition exacerbates these effects of inflammation [189].

Protection strategy

Improving vaccine efficacy in elderly. Elderly individuals are more prone to severe infections and less responsive to vaccination than the young [190], in terms of the titer, efficacy, and affinity of antibody production [191] and responses which are characterized by shorter duration [192] due to immunosenescence [193]. The vaccination against seasonal influenza, pneumococcal disease, and reactivation of varicella zoster virus (VZV), in addition to regular booster shots against tetanus, diphtheria, pertussis, polio are recommended in the elderly. An early study revealed that the vaccination to influenza drops to 30–50% for those over 65 years of age [194], in addition vaccination to pneumococcal disease is recommended for seniors [195] and it could reduce 63.8% of pneumococcal pneumonia in elderly [196] and that 23-valent pneumococcal polysaccharide vaccine reduces the incidence of all pneumococcal pneumonia [197]. Herpes Zoster (HZ) is a major cause of hospitalization in the elderly, the recombinant vaccine containing AS01B adjuvant, has been licensed in 2017 [198], it elicits a robust and persistent memory response in older adults [199], because it induces antibody and T-cell responses in the elderly [200]. Efficacy of HZ vaccine is about 97% in the prevention of HZ in older adults [201]. Adjuvants such as AS01 can strongly activate elements of innate immunity [202]. These effects may underlie the strong, long-lasting efficacy demonstrated against herpes zoster even in very old individuals [203]. Vaccine efficacy against hepatitis B virus (HBV) and A virus (HAV), tick-borne encephalitis (TBE), is significantly reduced in vaccinated individuals $\geq$70–80-year-old [204]. Booster intervals should be shortened for persons over 65 years because of the rapid decline in antibodies with advancing age [103]. Development of vaccine adjuvants specifically designed to optimally stimulate the aging immune system, the most currently used in the elderly are MF59 and AS03, included in influenza vaccines, and AS02 used for the recombinant HZ vaccine [205].

Cytokines, hormones, and pharmacological intervention strategies. Restoration of the T-cell pool balance should be done by stimulating the production of naive T cells and exporting them to the periphery by using cytokines and hormones such as growth hormone and interleukin 7 [84]. **Montecino-Rodriguez and colleagues 2013** revealed that the manipulation of the concentration of various cytokines including interleukin-7, IL-2 and hormones such as sex steroids, growth hormone and keratinocyte growth factor (KGF) has been shown to be promising for the rejuvenation of aged thymus [84].

IL-7. IL-7 is a cytokine that is produced by stromal cells and the thymus. It plays a pivotal role in supporting thymocytes development, stimulates peripheral T-cell survival and expansion through the induction of Bcl-2. It is thought to influence T-cell progenitors directly [206]. Many experimental studies carried out in old animals reported that IL-7 reversed thymic atrophy, increased thymopoiesis improved thymic output, boosting immune function [207].

IL-2. Interleukin-2 aids in the development of thymocytes, the survival and proliferation of T cells, increases the proportion of thymocytes that differentiate into mature T lymphocytes. Many studies suggested that it reverses thymic atrophy [208].

IL-15/IL-15Rα. IL-15 plays a critical role in the development and homeostasis of naive CD8 T cells, memory T cells, NK cells [209]; aging-related functional NK cell deficiency was completely reversed by injecting soluble IL-15/IL-15Rα complexes [210]. **Gangemi *et al*., (2005)** found higher levels of IL-15 in ultralongeval subjects denoting their strong immune system that is able to defend itself from infections through efficient immune-inflammatory responses which is crucial for their longevity [211].

Gene therapy intervention. Telomere length could be restored by reprogramming telomeres to increase the cellular life span which can be induced by using pharmacological agents or gene therapy in order to increase telomerase activity [212].

Adoptive therapy. Adoptive therapy is based on the replacement of senescent cells with effector or naive cells [213].

Hormone treatment

Fibroblast growth factor 7 (FGF7) .
Aging is associated with increased expression of the tumor suppressor gene Ink4a, (**Montecino-Rodriguez *et al*., 2013)** and his working group showed that fibroblast growth factor 7 administration (FGF7) which is a hormone that acts on thymocytes, down-regulates (Ink4a) in T cell progenitors and rejuvenates a partial part of the involuted thymus [84] and reverses the effects of aging [214].

Dehydroepiandrosterone (DHEA)
Dehydroepiandrosterone (DHEA) is a steroid hormone that is important for the functioning of immune system [215], by aging DHEA levels decline markedly [216]. A study released by **Prall and Muchlenbein, 2015** revealed that the presence of DHEA levels in the saliva

has a bactericidal activity, and acts as a measure of innate immune function [217]. Supplementation with DHEA improved immune parameters, including monocyte levels, B- and T-cell function, and NK-cell levels [218].

Natural products strategy that improves immune system in elderly

Probiotics. Probiotics may have a particular application in elderly populations, especially in terms of protection against infections and perhaps also in the prevention of several age-related diseases [219]; they restore the gut flora and reduce chronic inflammation and pathogen colonization within the host [220]. Many clinical trials have shown that probiotics enhance immune function in reducing the recurrency and the severity of infectious diseases [83]. A study by Toward *et al*. observed that *Bifidobacteria* decreases after 60 years of age, and this decrease was correlated with the occurrence of immunosenescence [221]. The administration of *B. bifidium* exerts an anti-senescence by reducing p16 expression in thymus and spleen; additionally, it has antiinflammatory effects (lower IL6 and TNFα levels) in old mice [222].

Yogurt. Yogurt has immunostimulatory effects. **Maydani and Han** stated that increased yogurt consumption, in immune compromised populations such as the elderly, enhances the immune response, and increases resistance to immune-related diseases [223]. A study by **Nagai** revealed that yogurt intake increases interferon-γ production and augments the natural killer cell activity in his experimental design [224]. Another study in humans showed that yogurt's bacterial components were able to decrease the incidence of the common cold in elderly people when administered daily [225].

Beta-Glucan. Beta-glucans are polysaccharides found in the cell walls of fungi, bacteria, oats, and algae. They are immunomodulators of immune activity with notable anti-tumor and antimicrobial properties [226], medicinal mushrooms such as Reishi are rich in Beta-glucans [227]; they have anti-tumor, and cell-killing effects. A portion of beta-glucan reishi polysaccharides has been found to stimulate both innate and adaptive immune responses [228], regarding innate immunity it was found to enhance both the killing and phagocytic activities of NK cells [229] and macrophages [230]. Regarding adaptive immunity it was found that beta glucan have the ability to influence T-cells activation and proliferation [231, 232] and B cell to proliferate and increase the secretion of immunoglobulin [233].

Cistanche deserticola (C. deserticola). It is a plant used in traditional medicine as a remedy for chronic infections. Many studies on aged animals observed that an extract of this plant extended lifespan and reversed many laboratory indicators of immune senescence, such as the increases in the population of naive T cells and NK cells, reductions in memory T cells in the peripheral blood, and decreased levels of the inflammatory cytokine interleukin-6 (IL-6) [234]; increased helper T cells, and improved NK cell activity [235].

Pu-erh tea extract. An early study on aged mice [236] revealed that supplementation with Pu-erh tea extract increased the fraction of naive T cells CD8(+)CD28(+) whether helper or cytotoxic T cells, and NK cells. In addition, elevated levels of the inflammatory cytokine IL-6 decreased by 43% [236], increased the resistance to infection and cancer in aging individuals [236]. Another study by (**Chu, 2011)** found that the Pu-erh tea extract decreased CRP, TNF- α, and IL-6 while levels of IL-10, an anti-inflammatory molecule, increased [237].

Garlic Extract. Garlic has immune-modulating and immune-stimulatory properties, as well as anti-tumor effects [238], it stimulates immune function by increasing macrophage activity, and production of T and B cells [239] as well as increased proliferation and activity of cytotoxic T-cells and NK-cells [240]. A recent study found that garlic supplements reduce the number, duration, and severity of upper respiratory tract infections [239] and it was associated with reduced cold and flu severity [240].

Quercetin. Quercetin, a bioflavonoid found in foods such as onions, apples, berries, and green tea, has potent antiinflammatory and free radical-scavenging properties. It has been shown to induce cell death in senescent cells, decreasing their numbers in human fat tissue cultures [241].

Tomatoes. Tomatoes are rich in lycopene [242]. **Riso *et al*.** stated that lycopene found in tomatoes slows down aging by stopping free radicals from binding with oxygen, a process that slows immune building, cleansing, and repair, and that consumption of tomatoes has been shown to be associated with a lower risk of several types of cancer [243]. Another study found that TNF-α levels were 34.4% lower in the subjects who drank tomato juice in comparison to those who do not [244]. These studies pointed out to the potential antiinflammatory effect of tomato [245].

Berries. Berries and their phytochemicals are immunomodulators that delay cancer development and contain a wide spectrum of phytochemicals that influence the functions of multiple immune cells and many aspects of cancer immunity [246] by boosting T cells to recognize tumor cells and destruct it. Recognition occurs after dendritic cells present antigen, such as tumor antigen, to T cells, generating an adaptive response [246]**.** NK cells are an essential component of innate immunity against cancer development [247]. **Pan *et al*., 2018** demonstrated that an increased number of NK cells and enhancement in their cytotoxicity occur after black raspberry intervention [246].

Brocolli. Carr and Maggini , 2017 showed that sulforaphane, which is a key bioactive compound in broccoli, has the capacity to slow the biochemical

process of aging [248] by increasing the expression of antioxidant genes [249] in addition it was demonstrated that Kaempferol, which is a flavonoid in broccoli, has a strong anti-inflammatory capacity [250].

CLINICAL TRIALS TO REJUVENATE IMMUNESENESCENCE

A National Institute of Aging sponsored randomized trial of a 2 year caloric restriction (CR) regimen in healthy humans (CALERIE) revealed that CR slow of biological ageing by reducing cardiovascular disease risk biomarkers and decreasing the levels of pro-inflammatory cytokines [251, 252]. Another study with 125 older subjects, RISTOMED, observed that Mediterranean diet has an anti-inflammaging effect [253]. Regarding probiotics a study on aged individuals reported that probiotic consumption for 6 months increased the number of naive T cells and decreased the number of senescent CD8 $CD28^{null}$ T cells [254]. Another trial revealed that healthy seniors that consume fermented dairy product for 3 months have a reduced risk of respiratory infection [255]. Regarding vitamins, a study by **(Shelbaya *et al*., 2017)** observed that the majority of elderly that live in nursing home or homebound are at risk of developing vitamin D deficiency because of lack of exposure to sunlight [256]. Concerning exercise (**El–Sabbagh and colleagues, 2015**) revealed that TNF alpha and CRP that are responsible for low grade inflammation in elderly were decreased significantly after training in aged healthy Egyptians [257]. Another study showed that the exercise intervention gave a significant benefit with respect to antibody titer prior to an influenza vaccination and that exercise can improve immune responses and specifically vaccination in the aged [258].

CONCLUSIONS

The fountain of youth is not a myth. After all methods explored in this review as current evidence underlines the importance of consuming a healthy diet best exemplified in the Mediterranean diet "which contains all the essential micronutrients", exercising, avoiding stress and sleeping well would slow down immunosenescence but are unlikely to reverse the decline of immunity completely, because they are only targeting a specific aspect of immunosenescence rather than stopping it from occurring. Nevertheless, improvement in immune function is beneficial to the elderly population, hence improving the quality of life in seniors.

RECOMMENDATIONS

By discussing the different aspects of immunesenescence and the strategies that can reduce it we recommend:

1. By easing stress cortisol levels decrease and sleeping patterns will be improved thus improving immune function.
2. Eating healthy nutrients, such as fruits, vegetables rich in beta-carotene, vitamins C and E, and zinc.
3. Probiotics are very important because they protect against infections and prevent several age-related diseases.
4. Regular physical activity promotes circulation and relaxes the body and mind. As walking, yoga classes are anti-immunesenescence and anti-inflammaging therapy that boost a senior's immune system performance .
5. The elderly should receive regular booster vaccines with shortened vaccination intervals to maximize their immune response, especially vaccination against seasonal influenza, pneumococcal disease, and reactivation of varicella zoster virus (VZV), in addition regular booster shots against tetanus, diphtheria, pertussis, polio.
6. As elderly thirst less so they must stay hydrated because water keeps mucous membrane moist and lowers the chance of colds.

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