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*Mini-Review*

# Physiological consequences of immune aging at organs level: A mini-review

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Aging is a discrete phenomenon and hard to understand. A coordinated and gradual loss of structure and function causes impaired responsiveness at cellular and organ levels. It makes an aged individual prone to several chronic diseases and opportunistic infections. The failed interplay among different organ systems is what orchestrates aging. Simultaneously, the involvement of more molecular participants makes it more challenging to understand and examine. This mini-review comprehensively reviewed physiological changes in immune aging and their correlation with overall aging anomalies.

**Keywords:** Infection, Inflammation, M1/M2 Macrophage, Oxidative stress, Senescence associated secretory phenotypes (SASP)

## Introduction

The field of 'immunophysiology' is not new but has not been sufficiently explored in every dimension. Deteriorating physiological parameters with growing age are known; however, its relationship with inflammaging has not been established. Their causal relationship requires in-depth analysis. This is quite certain that modulation in the immune system does affect the physiological functions of various organs. Physiological deterioration with aging is also evident[1,2]. However, how various interactors of aging-immune components affect physiological aspects requires a focused investigation. In the present review, we aim to provide an overview of deteriorating physiological parameters at the organ level and their associations with immune aging, particularly in inflammaging.

### Aging Muscle: an elevated M2 macrophage may dampen muscle regeneration and recovery

The aged muscle becomes weaker and more prone to damage. Moreover, recovery and regeneration are diminished, which correlates with reduced muscle mass in aging. A decline in the serum level of sex hormones, including estrogen, testosterone, and androgen, is positively associated with a decline in muscle mass and elevated sarcopenia[3]. Existing pieces of evidence suggest a potential role of chronic inflammation in muscle weakening and sarcopenia[4]. Przybyla *et al*.[5] have shown that aged muscles show the same level of CD68+ macrophages compared to young ones after the injury. Also, report show that aging does not have an essential role in deploying myeloid cells in young vs. old muscles during muscle injury. However, their capacity to heal in old muscles may be questionable. It is pertinent to mention that augmented muscle fibrosis in aging[6] can also be correlated with M1/M2 macrophage dichotomy and elevated levels of inflammatory markers.

Furthermore, there is reduced leukocyte recruitment in prolonged and extensive injury. This could be because the assessed level of injury to the old muscle is much more extensive than the young ones[7], which might impair the recruitment and function of leukocytes, thus delaying muscle regeneration and diminishing muscle force. Additionally, Chronic inflammation, i.e., 'inflammaging,' is a critical feature of aging with proinflammatory cytokines like TNF-α, TGF-β and IFN-γ in dominance[4]. Besides, a paradoxical antinflammatory cytokine IL-10 increase in aging is well established[8]. SASPs interfere with the self renewable capacity of muscles either by CCN1 mediated mechanisms or via PI3/Akt pathway[9], thus contributing towards muscle weeknes an dampened function in aging. As discussed earlier in the section, the recruitment of macrophages after muscle injury can regulate muscle regeneration after injury. However, a biased M2 phenotype of recruiting macrophages may dampen muscle regeneration and recovery. A proinflammatory milieu has been reported to promote the M1-biased phenotype.

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Oppositely, old muscles feature elevated M2-biased phenotype (CD206+ high, CD163+high)[10] that can be correlated with the paradoxical abundance of IL-10 in aging. This biased increase in M2 phenotype can also contribute to muscle fibrosis in aging[11].

**Aging Liver: Compromised oxidative and proliferative capacities gradually get accumulated**

The aging liver undergoes several degenerative changes including; decreased blood flow, decreased LDL cholesterol, increased activity of alkaline phosphatase, accumulation of lipofuscin bodies, and hepatocyte polyploidy, where liver structure and function decline. An increase inthe production of proinflammatory molecules is quite evident[12]. Almost 40% of the total volume loss in the blood is contributed by a decrease in blood volume in the liver. A reduction in albumin and CRPs that regulate the oncotic pressure and blood volume are correlated with aging. Changes in cellular architecture due to the deposition of unwanted substances throughout life can cause the thickening of sinusoidal endothelial cells, thus constricting the molecular exchange across the blood barrier[13]. The gradual accumulation of liver toxins due to compromised oxidative capacity and anti-proliferation complexes like CEBP-α-Brm-HDAC1 help reduce the proliferative capacity of liver cells in aging[14]. Accumulation of senescent cells in the liver with aging causes the release of anti-proliferative factors, including p21, p16 and p53, which can cause tissue damage and chronic liver diseases[15]. These senescent cells also result in increased transportation of conjugated bilirubin and contribute towards insulin resistance via Akt signaling, thus causing perturbed liver function in aging. Alteration in autophagy for liver resident macrophages has been shown to increase the production of proinflammatory cytokines in aging, which correlates with age-related morbidity, and an increase in oxidative stress[16]. SASPs contributes towards these cytokines and promotes faty cell accumulation and steatosis in aged liver[17]. Accumulation of oxidative stress contributes to the progression of age-associated fatty liver diseases[18]. Aging promotes cell adhesion markers like ICAM-1 production, which causes inflow/deposition of inflammatory cells at hepatic sinusoidal walls, thus promoting dysfunctional microcirculation, macrophage aggregation, and impaired blood flow[19]. Increased ICAM-1 expression has also been correlated with the increased production of IL-6 and IL-1, thus contributing to heightened liver inflammation and increased CD68+ macrophages in the sinusoidal area in aging[20]. This interplay between the availability of oxidative stressors and pro-inflammatory molecules (TNF-α, IL-1 and IL-6) in the liver contributes to anomalous maintenance of live function in aging.

**Aging Heart: Persistently inflamed endothelial cells produce proinflammatory cytokine and affect cardiovascular loadgradually**

The aged cardiovascular system shows a radical morphological and functional shift. An increase in the stiffness of large vessels in the heart causes elevated systolic blood pressure and decreased diastolic pressure, thus causing increased left ventricular load[21,22]. Attenuated calcium flux in aging causes reduced left ventricular compliance and delayed relaxation. Aging promotes mineralization of collagen and accumulation of advanced glycation end products (AGEs), that allows the deposition of ECM and glycosamineglycans, thus causing firbrosis in resident cells[23]. Fibrosis in resident myocytes and calcified valves can cause decreased reactivity of baroreceptors and chemoreceptors, reducing cardiac output. Aged myocytes show decreased sensitivity to β-adrenergic receptors. Dysfunctional endothelial nitric oxide synthase in aging myocytes results in a decrease in nitric oxide production. Subsequently, the amplified release of ROS leads to rigidity of vessels and vascular inflammation[24]. This vascular rigidity in aging has also been associated with increased glycosylated proteins, matrix metalloproteinase activity and angiotensin-2 responsiveness[25]. Accumulation of cholesterol-loaded immune cells, senescent cells, and excessive secretion of pro-inflammatory cytokines from aged endothelial cells cause insistent vascular inflammation, and there is evidence that the spread of vascular inflammation to other allied tissues can cause systemic changes in the circulatory system[26].

This persistent low-grade inflammation at the endothelium lining of blood vessels, induced by SASP accumulation, causes increased levels of adhesion molecules like ICAM-1 and VCAM-1[27] that induce leukocyte adhesion. Under prevailing inflammatory conditions, hyperactivated monocytes activate the leukocytes. Under these conditions, endothelial cells also adapt to mesenchymal cells (endothelial to mesenchymal transition, EndMT), causing more monocyte adhesion due to increased adhesion molecules expressions and ECM deposition. This also allows access to deep in the vessel wall. All these changes gradually direct the migration of smooth muscle cells from tunica media into the inner

intima, where calcified plaque is formed under the influence of various inflammatory factors like TGF-β[28]. This increases the intima-media thickness (IMT) and promotes plaque formation. Alteration in cardiac vasculature, influenced by these immune-modulatory changes, thus leads to ventricular wall thickness causing ventricular hypertrophy resulting in compromised cardiac output and vascular load[29]. It can be further related to common age-associated cardiovascular conditions like arterial fibrillation. Age-associated chages in T-cell repertoire[30] have also been correlated with metabolic and immunological dysfunction[31] leading towards cardiac dysfunction[32]. It can be concluded that failure of the endothelial compartment in aging can be targeted for therapeutic interventions in cardiovascular diseases.

**Aging Kidney: Proinflammatory cytokines gradually reduces kidney function**

Aging does not necessarily cause renal diseases. However, the kidney displays a discrete array of physiological and morphological changes that might contribute to renal pathology in aged individuals. The nephron function is declined with age, which correlates with the decline in the glomerular filtration rate[33]. Kidney resident podocytes undergo hyper-trophy with a limiting proliferation capacity due to the loss of nearby cellular niches in aging[34]. However, due to the gradual loss of nephrons, podocyte hypertrophy starts to fail, resulting in capillary collapse, periglomerular fibrosis, and podocyte detachment[34]. Age-dependent overproduction of proinflammatory cytokines causes changes in vascular motor activity. Likewise, stress activators can exaggerate vascular motor changes[35]. Increased levels of endostatin, thrombospondin-I, and the decline in vascular endothelial growth factors in aging cause a chronic loss in perfusion, capillary network, and nephron[36]. Loss of pericytes in aging kidneys has also been correlated with the deteriorated capillary architecture in aging[37]. Elevated mitochondrial aberrations in resident tubular cells cause the accumulation of spoiled macromolecules and enhanced release of oxidative stressors, thus limiting the filtration capacity of renal tubules[38]. Exposure to chronic inflammatory milieu by the circulating blood in the kidney tends to challenge renal parenchymal cells constantly, thus causing accumulation of cells with the senescence-associated secretory phenotype (SASPs)[39]. The transient presence of these SASPs in the kidney somehow increases renal recovery and promotes immune surveillance. However, age-associated aberrant accumulation of SASPs in renal walls promotes immune filtration and recruitment of immune cells via the increased adhesion molecules, thus reducing renal recovery[40], promoting renal fibrosis, and age-related glomerulosclerosis. Conclusively, immune filtration and SASPs insult the aged kidney and reduce its function significantly.

**Aging lungs: Persistent inflammation reduces vital capacity of lungs**

The epithelial components of the respiratory tract are the first line of defense against upcoming pathogens. The coordinated action of goblet cells, club cells, ciliated columnar cells, and club cells within the respiratory epithelium decides the fate of invading pathogen[41]. The resident and employed immune cells derived from lymphoid and myeloid progenitors[42] carry forward this action. The respiratory epithelial cells can also secret cytokine, thus affecting the activity of proximal leukocytes[43]. The low-grade inflammation in aging has also been correlated with increased *Streptococcus pneumoniae* colonization in the upper and lower respiratory tract, thus causing frequent pneumonia-like symptoms[44]. Antigen-macrophage interaction helps process the immune signal and responds by releasing anti-/pro-inflammatory molecules. Local epithelial cells, alveolar macrophages, and interstitial macro-phages play a crucial role in fortifying respiratory response. However, studies have reported poor number and activity of alveolar macrophages in aging, causing a decline in various cellular functions, including inadequate response to pathogens, reduced phagocytosis, and flawed TLR signaling. Monocytes from aged/older adults show reduced TLRs expression with impaired detection of PAMPs[45]. On the other hand, when stimulated, they tend to produce imbalanced proinflammatory cytokines, i.e., increased TNF-α and IL-6. Interestingly, Alveolar fluid from older adults has higher levels TNFs, complement proteins, and IL-6, contibutede by SASPs, adding to the deregulated innate immunity[46].

Additionally, aging interrupts cellular signaling, i.e., RIG-1 signaling, disrupting type 1 interferon expression and leading to poor antiviral response at the organ level. Resident neutrophils that make a second line of defense are found abundantly in the lower respiratory tract of older adults and contribute towards age-associated inflammation. This has been implicated in influenza-associated mortality in the aged lung. An unusual PI3K signaling in aged pulmonary neutrophils has been positively correlated to tissue damage and aberrant inflammation[47].

Similarly, lung resident dendritic cells display impaired cytokine production, antigen presentation, and phagocytosis in aging. Persistent inflammation in the lower respiratory tract reduces the vital capacity of respiration, resulting in poor oxygenation and increased compensatory respiratory rate. Overall, age-associated decline in pulmonary function, mediated by various intrinsic factors affect the body as whole and promote severe COPD consequences[48].

**Aging brain: Synaptic failure and inflammation**

Aging causes accelerated cognitive decline and memory loss, making older people more vulnerable to neurological abnormalities and cognitive dysfunction. Both environmental and molecular factors contribute to the changes in the anatomical and morphological architecture of the aged brain. Neurodegeneration with cognitive decline and motor dysfunction is accompanied by systemic inflammaging[49]. Here, the blood-brain barrier (BBB) acts as a limiting boundary that separates the brain from the rest of the body. A persistent release of inflammatory cytokines such as TNF-α, IL-1 and IL-6, etc., increases BBB permeability resulting in the recruitment of inflammatory cells. A gradual dysfunction of microglial cells also contributes to inflammation in the brain. Presence of senescent-associated microglial cells in post-mortem Alzheimer's brain has been positively correlated with neurodegeneration[50]. Microglial cells are homeostatically maintained by the interactions with neurons mediated by ligands such as CXCL1, CD47 and CD200. Accumulation of plaque-associated proteins, including amyloid-β, chromogranin, synaptophysin, tau, synapsin, EP-10 antigen, p65, along with vesicles, at synaptic junction makes synapse swollen and induces a loss in synaptic activity in aging[51]. This results in slowing down of nerve conduction leading to delayed response time. Though, delayed response time may also happen due to other reasons not discussed here. Any trauma in old age or age-related changes in the cerebral vasculature cause white matter injury resulting in a dysfunctional blood-brain barrier[52]. Accumulation of clonally-expanded-antigen-trained T cells near the deteriorated BBB has also been positively associated with aging and age-associated neurodegeneration[53]. Reports suggest older individuals recovering from or persisting with cardiac or respiratory conditions are frequently accompanied by a cognitive decline in aging. Besides, chronic cardiac abnormalities and stroke expedite the advancement of neuronal diseases like Alzheimer's and vascular dimentia[54]. Thus, it can be stated that aging promotes chronic inflammation, and incomplete activation of immune cells in the aged brain can create an inflammatory state and contribute to microglial cell dysfunction.

Figure 1 summerizes the effects of aging, in terms of immunity, on various organ systems of humans.

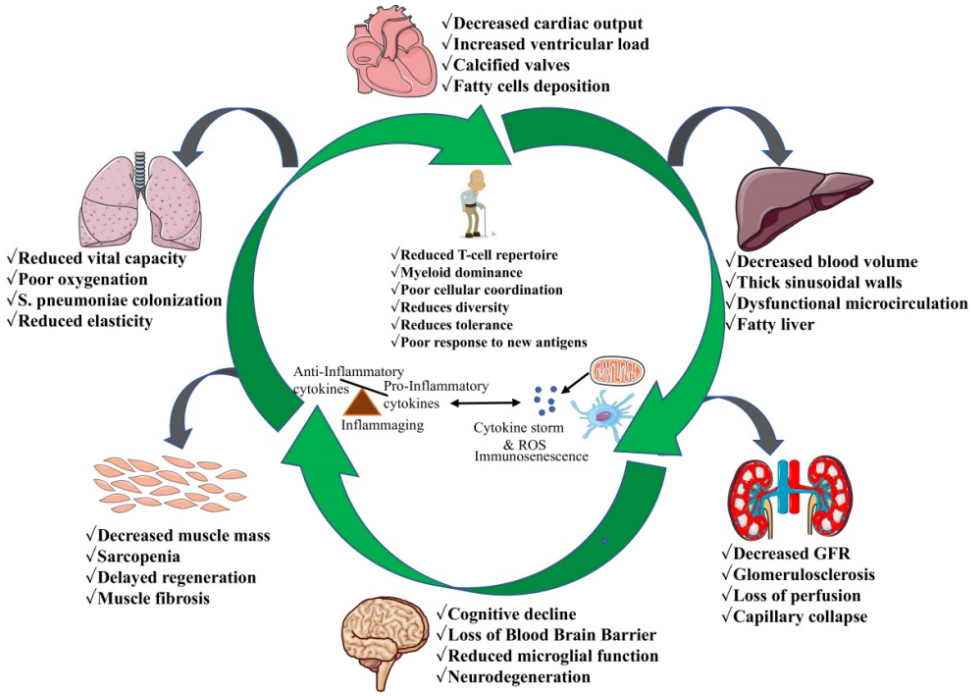


Fig. 1 — Schematic representation of the effects of aging on various organ systems of human.

## Conclusion

Overall, aging does affect the physiological functions of different cells, and collectively, the same is manifested at organ levels. However, aging of the immune system can also specifically deteriorate physiological functions. The decline in physiological functions due to an aging immune system may not coincide with physical aging and sometimes even precedes. It may show loss of vital functions, aggravating overall aging. This aspect of an aging immune system has yet to be studied in detail. This review highlights the avenues for detailed study to slow down the loss of physiological function by addressing the inflammaging, which may improve the well-being of aged individuals. The immunological rearrangements in aging may boost physiological functioning and reduce age-associated mortality.

## Conflict of interest

None declared.

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