# PHYSIOLOGY OF AGING

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**Abstracts:** Aging is characterized by physiologic changes which lead to decline in biological functions and a decrease in the ability to adapt to metabolic stress. Decline in cognitive function, increase in the systolic blood pressure with a wide pulse pressure, increase in alveolar-arterial oxygen gradient, loss of functional nephrons with progressive decline in renal function, and menopause in women, are some of the hallmarks of aging. Telomeres, structures at the end of chromosomes, shorten with age, leading to loss of protective mechanisms in the human body. The telomerase theory is a key theory which explains aging in humans. In addition, accumulation of toxic free radicals, and decrease in the function of mitochondria, leading to apoptosis, are other key contributors to aging in humans. Aging is associated with many diseases like cataracts, hearing loss, diabetes mellitus, depression, and dementia. Geriatric syndromes include frailty, urinary incontinence, falls, delirium, and pressure ulcers. Loss of muscle mass (sarcopenia), and a decrease in the functional life space- a measure of spatial mobility, are associated with the frailty syndrome. Regular exercise, balanced diet, adequate sleep, good psycho-social support, and the habit of participating in activities, which one cherishes, facilitate successful or health aging.

## Introduction

Aging is an unavoidable and a natural progression of the human life cycle. Aging is defined as progressive physiological changes in a living being leading to decline of biological functions and ability to adapt to metabolic stress[(1)]. Aging leads to increased risk of debility, morbidity, and death. It is characterized by chronic, normal culmination of loss of normal regenerative and bio protective mechanisms in an organism[(2)].

Gerontology is the study of the aging process- evolutionary and individual perspective. Senescence is manifestations of the aging process. Life expectancy in the world, at birth is 73.2 years, more in females compared to males. Life expectancy has increased due to improved health care, awareness of healthy lifestyle and nutrition.

It is important to understand the clinical and epidemiological relevance of the process of aging for giving special care and management.

Systemic Changes with Aging

Neural System:

With the advancement of age, there is a gradual decline in cognitive function. This decline should be differentiated by all concerned, from the profound loss of cognitive function that occurs with Alzheimer's disease. There is a subtle decrease in the visual, auditory, olfactory, and gustatory function with age. Gait and balance also deteriorate. Hence, it is critical to prevent falls in the elderly.

Muscle System:

There is a loss of the skeletal muscle mass with normal aging. This phenomenon is called by scientists as sarcopenia. This results in a decrease in the lean body mass. There is a decrease in the strength and elasticity of skeletal muscles. In addition, there is a decrease in the number of mitochondria, capillary density, and cellular enzymatic activity. This apparatus is needed by the cells for the greatest extraction of oxygen during exercise, which suffers as a result.

Cardiovascular System:

With advancing age, there is calcification of the blood vessels. This '*stiffening'* of the vascular bed is defined as 'arteriosclerosis'. This process results in loss of compliance of the arteries. This loss of the '*Windkessel Effect'* impairs the normal diastolic run-off of blood, compelling the heart to generate more force to sustain blood pressure. Hence, the systolic blood pressure becomes elevated with advancing age. This is one of the hallmarks of aging. The diastolic blood pressure is still unaltered, resulting in a wide pulse pressure.

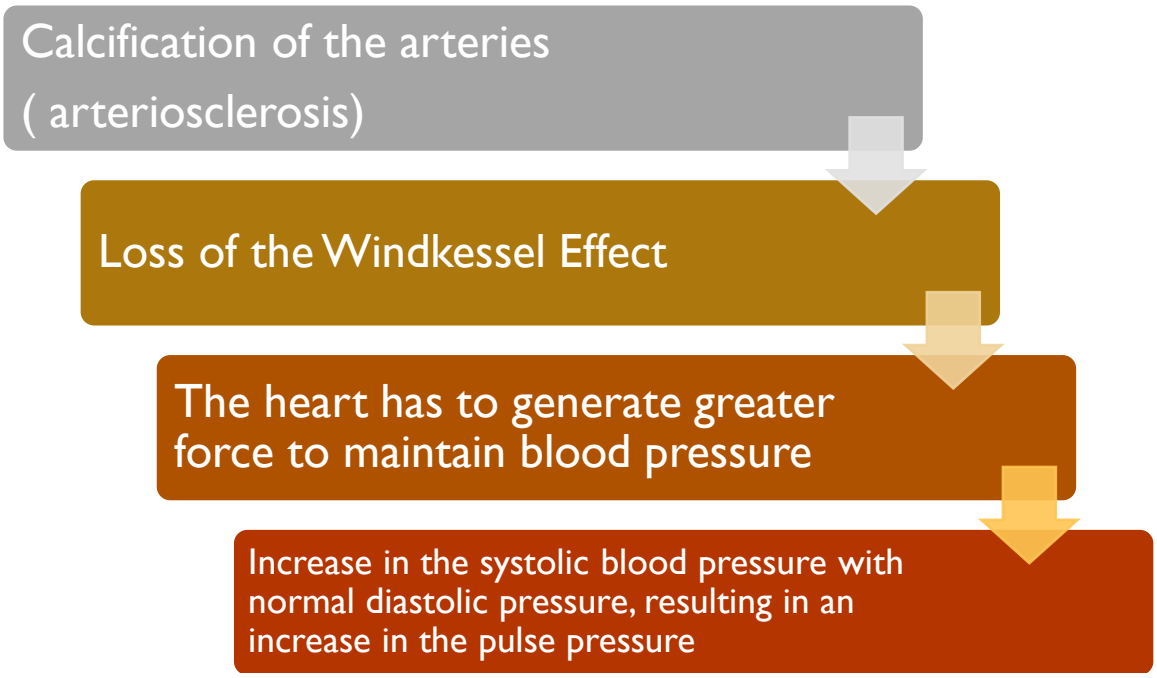



Fig. 1. Change in the blood pressure with aging

Pulmonary System:

As a person ages, the recoil tendency of the alveoli decreases. Hence, there is a corresponding increase in the lung compliance. This is complicated by the decrease in strength of the respiratory muscles and changes in the rib cage and spinal column. Hence, the compliance of the chest wall decreases.

One of the hallmarks of aging is an increase in the difference between partial pressure of alveolar oxygen ($P_{AO2}$), and that of the arterial oxygen ($P_{O2}$). This so-called A-a oxygen gradient increases, because of a mismatch between pulmonary ventilation and pulmonary perfusion, called as a ventilation-perfusion mismatch. This phenomenon occurs because the number of functional alveoli decreases.

Renal System:

After the age of 40 years, the number of functional glomeruli decreases by ten percent every decade. Age-related changes in the renal arteries and afferent arterioles decrease the renal plasma flow. Hence, there is a decrease in the creatinine clearance by about 30%. The creatinine clearance is an index of the glomerular filtration rate. In addition, the ability of the kidneys to concentrate and dilute the urine decreases. However, the basal water and electrolyte balance are not significantly altered in the body with aging.

The risk of dehydration increases with aging. There are three reasons for this vulnerability. Firstly, the ability of the kidneys to concentrate urine iscompromised. Secondly, thirst is impaired. Thirdly, there may not be the requiredincrease in plasma anti-diuretic hormone with an increase in serum osmolality.

Gastro-Intestinal System:

There is a subtle decline in the co-ordination of the swallowing reflex. Coupled with an increase in the gastro-esophageal reflux, the risk of aspiration pneumonia is enhanced. The colon tends to thicken with aging. Hence, the force of contraction needed for defecation is increased. This phenomenon increases the risk of the formation of diverticula. The latter are outpouching from the intestine where feces are likely to accumulate. These outpouchings might burst, resulting in peritonitis. The ability of the small intestine to absorb calcium is decreased.

Coupled with this, adults succumb to the tendency to get less sunlight. This can lead to a precipitous decline in the bone mineral density with advancing age. There is a subtle decline in liver function. Hence, the ability of the liver to metabolize drugs is decreased. This can lead to drug toxicity.

Endocrine System:

The most dramatic consequence of aging in females is the cessation of the ovarian function. This heralds the onset of menopause. The loss of estrogen results in a couple of major harmful effects. Firstly, loss of the bone mineral density (osteopenia), which can progress to a profound loss, thereby resulting in osteoporosis. Secondly, the risk of cardiovascular disease is enhanced in females after menopause.

The decline in male reproductive function is not so profound, and most men can remain fertile into their eighties.

There is a decrease in insulin sensitivity, and an increase in the risk of developing type 2 diabetes mellitus. Growth hormone secretion decreases with advancing age. Experts advocate hormone replacement therapy with growth hormone to counter the effects of aging[3].

Process of aging:

According to Gompertz, death may occur due to two generally co-existing causes- chance, without previous disposition to death or deterioration and other one, deterioration or increased inability to withstand destruction[4].

Normally, throughout the life, most of the cells of our body proliferate, but there is a limit to replication. As age progresses, cell proliferation slows down.

On a cellular level, as cells divide, telomeres on DNA shorten[5]. Telomeres are structures present at the ends of chromosomes. This causes decrease in protective proteins which are present at distal ends of telomeres, leading to loss of metabolic and replicative functions. Progressive telomere shortening leads to cell senescence. Gradual accumulation of senescent cells coupled with deteriorating cellular activity, produce changes related to ageing.

Factors like exercise, stress, sleep, mutations can also reduce telomere length leading to premature biological aging. Researchers can use telomere length to find the biological age of an individual.

As age progresses, there is accumulation of unrepaired damage of cells leading to tissue dysfunction and senescence. Our body's homeostatic mechanism tries to repair the damage, but after several decades, the mechanisms weaken, and are not able to withstand damages. Damage to cells can be due to reactive oxygen species and reactive nitrogen species or due to toxins, irradiations.

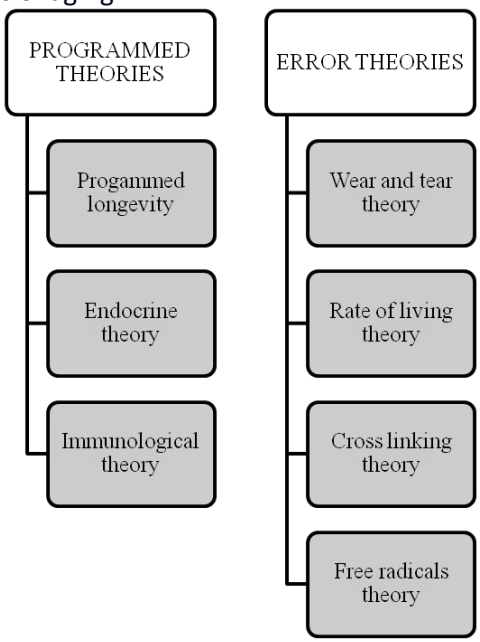
Interactions of DNA damage, protein damage, dysregulation of cellular signaling, mitochondrial dysfunction, oxidative stress, are features of aging[6].

Theories of aging.

There are various theories of aging, which can be classified under two broad categories[7]:

1) Programmed theories of aging.
2) Damage or error theories of aging.

Figure 2: Theories of aging.



d) Programmed theories-

According to these theories, aging occurs due to routine body biological processes which can be regulated by genes. There is deterioration of health and aging leading to limited lifespan which gives evolutionary benefit. As age progresses, many cells stop dividing or commit suicide- apoptosis. According to the Hayflick phenomenon[8], cells keep on dividing till they are no longer able to divide- triggering apoptosis.

There are three sub-categories of programmed theories:

a) Programmed longevity: According to this theory, aging occurs due to the switching on and off, of certain genes. Each cell has a genetically programmed genetic code in its DNA. These codes are responsible for diseases, causes of death and aging. Biological rhythms like circadian rhythm lose rhythmicity with age.

b) Endocrine theory: Hormones are responsible for aging. Decline of hormones occurs due to decrease in the activity of the hypothalamus, which is a major source of hormones of the body. Releasing and inhibitory hormones of hypothalamus control all major glands of the body like pituitary, thyroid, adrenals, gonads. Hormones like oestrogen, growth hormone, and melatonin decrease. Hypothalamic-pituitary-endocrine axis get deranged as age progresses.

c) Immunological theory: Immune system of our body deteriorates over time leading to increased susceptibility of the body to various diseases, thus leading to aging. As age progresses, the thymus gland shrinks, lymphocyte function is altered, cellular and humoral immunity decreases, leading to infections and cancers. Auto-antibodies are formed against the body's own cells, leading to autoimmune disorders.

2) Damage or error theories- According to these theories, aging occurs due to wear and tear leading to deteriorative processes in the body.

There are four categories of error theories.

a) Wear and tear theory: Aging occurs due to wear out of important tissues of our body as life progresses. Cumulative changes occur in cells as they age, damaging cellular metabolism. Aged cells lose their ability to counteract mechanical and inflammatory injuries.

b) Rate of living theory: More the body's rate of basal metabolism, shorter the lifespan.

c) Cross-linking theory (Glycosylation theory): As age progresses, cross-linked proteins accumulate, damaging the vital tissues leading to aging. Over a period, biochemical processes create connections which are not normally present.

d) Free radicals' theory: Free radicals are any molecules having free electron, which can destroy healthy molecules. Free radicals and superoxide damage the delicate machinery of the cells causing loss of functioning of cells, leading to aging. Improper diet, some drugs etc. can increase free radicals in the body, thus promoting aging.

Super oxides or free radicals react with proteins, lipids, DNA, RNA, mitochondria, causing cellular damage. Damage to DNA can lead to malignancy, genetic modulation, and accelerated ageing. Lipid oxidation can alter membrane permeability.

**Other theories:**

* Orgel/error theory: As life progresses, errors in DNA, RNA, protein synthesis, keep on accumulating, leading to cell damage and death. E.g., X-ray radiation can lead to chromosomal abnormalities.

* Membrane Theory of aging[9]: As age progresses, the cell membrane loses its lipid content leading to impaired functioning of the cell. This can lead to impairment of the cell's ability to transfer chemicals, heat, and electrical impulses.

* The Decline theory: We all know that mitochondria are the powerhouse of the cell. Decline of this function can hasten aging. Hence, it is of utmost importance to preserve and enhance mitochondria via nutrients like acetyl-L-carnitine, NADH, vitamins etc.

* Disengagement theory[10]: This theory is more of a psychological theory. According to this theory, as age progresses, people tend to withdraw from society and vice versa. This is desirable for maintenance of social equilibrium. However, this theory has been criticized often.

* Activity theory[11]: As name suggests, this theory states that loss of activity in any form can lead to changes of aging. If people stay

active and keep social interactions, successful aging occurs. There is a positive relationship between activity and satisfaction in life, leading to a sense of self-concept and better quality of life. People can take up new activities as life progresses.

In the Clinic

Common conditions associated with ageing:

The common conditions associated with aging include hearing loss, cataracts, and refractive errors, back and neck pain and osteoarthritis, chronic obstructive pulmonary disease, diabetes, depression, and dementia. With advancing age, even four or more of these conditions can occur simultaneously in the individual[12].

Geriatric syndromes:

These include frailty, urinary incontinence, falls, delirium, and pressure ulcers[12].

*The Frailty Syndrome*

Frailty is a common clinical syndrome in older adults. It is associated with four major poor health outcomes like falls, incident disability, hospitalizations, and mortality. Frailty is theoretically defined as a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability of the individual to copewithdaily or acute stressors is severely compromised[13].

In the absence of a gold standard,frailty has been operationally defined by researchersas meeting three out of five phenotypic criteria showing compromised energetics:

-Low grip strength
-low energy
-slow waking period
-low physical activity
-and/or unintentional weight loss

A behavioral precursor for frailty syndrome is life space-a measure of spatial mobility. It is defined by researchers as the size of the area a person purposely moves through in his/her daily life, as well as, frequency of travel, in his/her daily life[13]. (Figure 3).

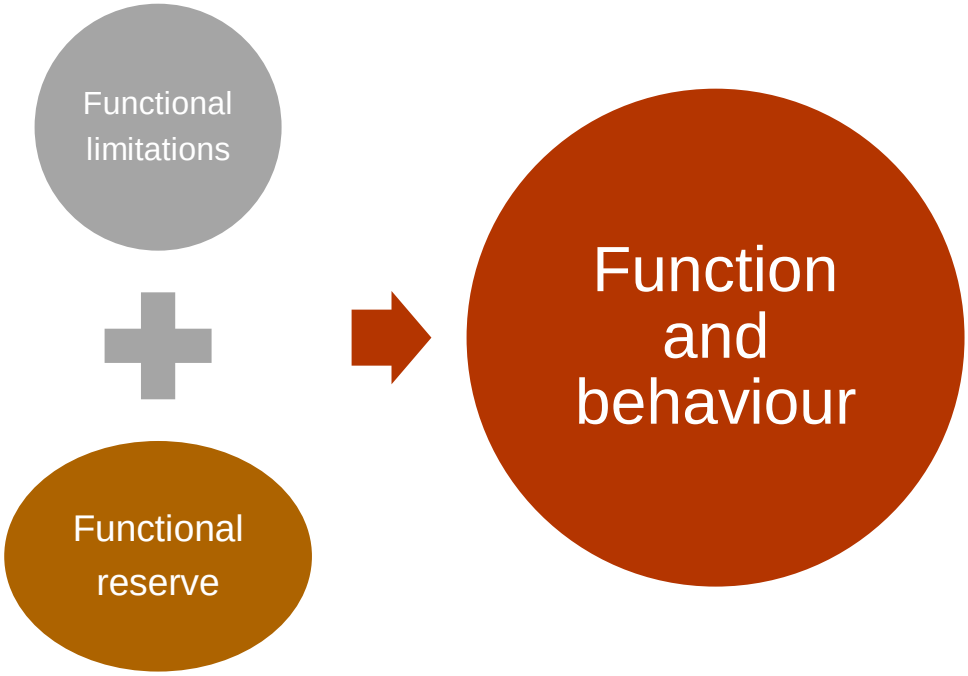



Fig. 3. Interplay of forces that affect the Frailty Syndrome

Successful or healthy aging

Jeanne Calment was one of the longest living women on record with a lifespan of 122 years. Shestarted the sport of fencing at the age of eighty-five; she was still riding in her triple digits. On her hundredth birthday, she walked around the town of Atles, France, thanking the people who had wished her a happy birthday. Calment's zest for life, and that she was able to relish it, captures a human wish:that we age as healthy individuals[14].

Successful or healthy aging *promotes the concept that aging is not an illness, but a natural phenomenon, and can be influenced by lifestyle, genetic and environmental factors*[3].The bedrocks of a healthy lifestyle like eating a balanced diet, exercising regularly.And abstaining from tobacco, are also critical for health aging. Supportive physical and social environments are vital for people to take part in activities which they cherish. The examples of a supportive physical environment include safe and accessible public buildings and transport, and places that are easy to walk around. Psychosocial support and growth are also crucial for a person to age gracefully[12]. (Figure 4).

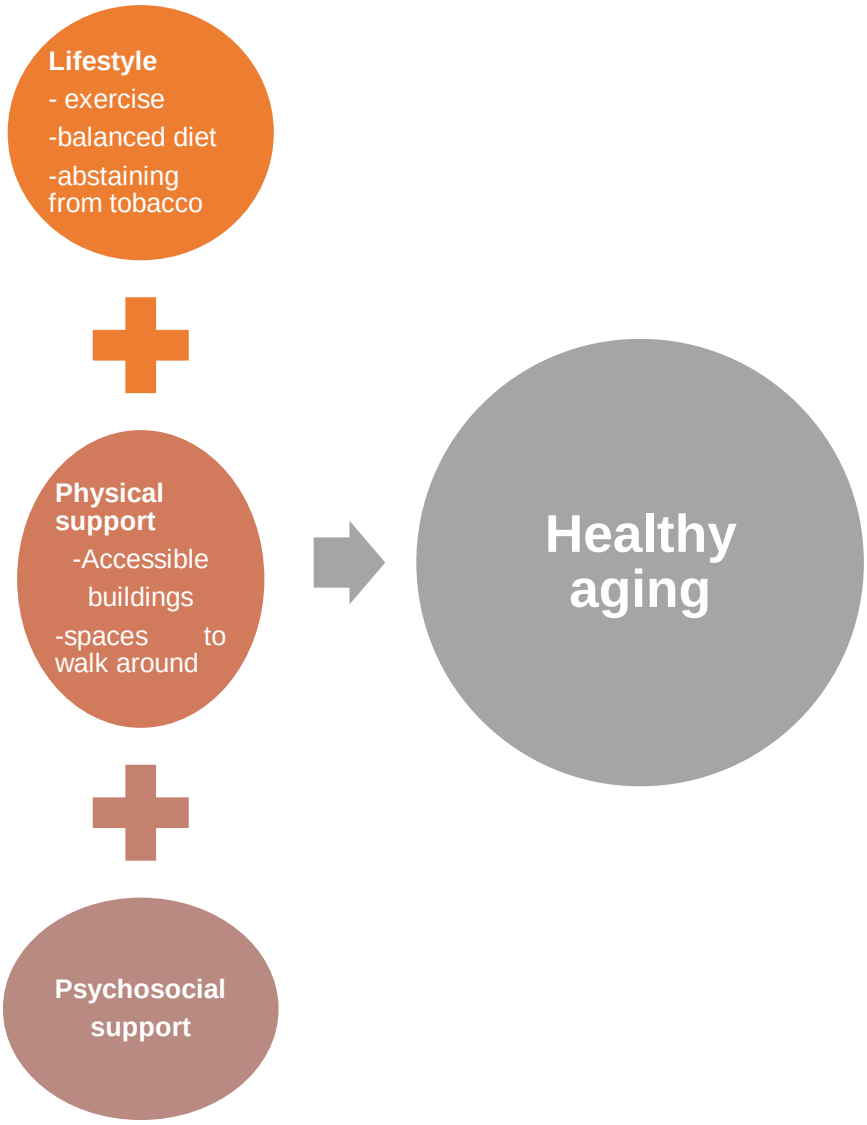



Fig.4. Essential requirements for healthy aging

To conclude, current evidence indicates that aging is an inevitable phenomenon in humans. It is associated with many overt and subtle deleterious effects. By leading a healthy lifestyle, participating in hobbies and maintain spatial mobility, a person can age gracefully.

Thus, whether one becomes old or not is not a matter of choice; however, how one lives in old age is!

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