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Review Article

Pathophysiology of human aging with a hint on sarcopenia: A review article.

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Abstract

Aging is a complex, time-dependent decline in human function, increasingly affecting the global population, particularly those over 65. With advancements in medical technology, lifespan has increased, but so has the prevalence of age-related disorders such as cardiovascular diseases, cancer, and neurodegenerative diseases. This decline is driven by cellular senescence, oxidative stress, and inflammation. Multiple theories of aging have been proposed, encompassing both programmed and damage-induced perspectives.

Many studies examine the biochemical and genetic mechanisms underlying the aging process, encompassing telomere shortening, genomic instability, oxidative stress, cellular senescence, and epigenetic changes. Aging significantly contributes to various age-related disorders, including neurodegenerative diseases and cardiovascular diseases. Key findings include the role of genomic instability due to DNA damage accumulation, the impact of reduced telomere length on cellular senescence, mitochondrial dysfunction related to energy production and ROS generation, and the decline in proteostasis leading to protein aggregation. Understanding these pathways may provide targets for interventions to delay aging and ameliorate related diseases.

Skeletal muscle aging (Sarcopenia) is characterized by progressive structural (muscle mass loss) and functional (muscle strength) changes. Although it is typically associated with advanced aging, it is now known to begin before the age of 60, Multiple biochemical and molecular changes in muscle structure, along with hormonal imbalances and other external stimuli, are the pathophysiology of sarcopenia.

Keywords: Pathophysiology, human aging, sarcopenia

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Introduction:

Human ageing is a complex time-dependent functional decline that lowers quality of life.[1] Globally, the average lifespan has significantly increased due to advancements in healthcare technology; nevertheless, this has additionally led to population ageing in parallel with a drop in the birth rate. The percentage of people over 65 is growing faster than any other age group worldwide. In addition, the UN predicts that one in six people will be over 65 by 2050, and this trend will cause the number of people over 80 to triple.[2] Aging can be defined as a progressive decline in cellular adaptation to internal and external impairment, combined with a physiological decrease in the biological activity of several organs. Senescence, additionally referred to as cellular aging, is the hallmark of ageing that involves a decline in cells' ability to regenerate themselves.[3]

A major risk factor for the development of several age-related illnesses is ageing. As the world's population continues to age, the number of aging-related diseases is also steadily rising. It is a major risk factor for the majority of chronic diseases that affect people, such as cancer, cardiovascular diseases (like stroke), and neurodegenerative disorders (like Alzheimer's disease (AD)). Reactive oxygen species (ROS) accumulation, which results in oxidative stress and inflammation, is the primary cause of cellular senescence[4]

A decline in immunity, with a reduction in basal metabolism, and a decrease in the activity of enzymes associated with antioxidant activity constitute some of the physiological processes that accompany aging. Many theories, such as damage and programmed theories, have been made up to combat the aging process concerning the various modalities of action. Age-related genes and the endocrine system may be the most pertinent subjects for programmed theories, which incorporate planned deterioration as people age. According to some scientists, aging is caused by an accumulation of damage, such as oxidative damage, mitochondrial DNA damage, and genome damage, rather than being programmed.[٥]

The underlying aging molecular mechanisms that differ between species remain under investigation, although the fact that aging is a process that happens in all species. The aging process is believed to be controlled by both genetic and environmental factors, concerning that environmental factors playing a significant role.[٦]

Many muscular disorders, including atrophic diseases with aging, are significantly affected by elevated levels of mitochondrial ROS.[7]

According to UN statistics, the percentage of adults over 65 increased from 6% in 1990 to an expected 9.3% in 2020. Healthy aging has come to be a key concern for both governments and society in both developed and developing nations, as the global population ages and lives longer. The "process of developing and maintaining the functional ability in older age" is how the WHO defines healthy aging. The functional ability, or the skills that allow everyone to be and do what they have reason to value, is the primary focus of this definition.[8] Hence the "health span" has not expanded in parallel with the life span.[9]

Consequently, focusing on "healthy aging" brought up many significant questions regarding the social sciences and life. Numerous advancements in the study of ageing have occurred recently, especially in the areas of conserved genetic pathways and biological processes.[10]

Pathophysiology of aging (Fig. 1):

Studies on aging have concentrated on deciphering the genetic and metabolic processes linked to aging, such as oxidative stress, cellular senescence, genomic instability, and telomere shortening. Age-related medical conditions such as cancer, musculoskeletal diseases, immune system disorders, cardiovascular diseases, and neurodegenerative disorders are also greatly influenced by aging[11] .

1. Genomic instability

Since the 1950s, the main cause of aging has been recognized to be the accumulation of DNA damage (somatic mutations) with age, because it disturbs cell homeostasis and leads to copy, somatic, and genome mutations, all of which exacerbate DNA damage . [12]

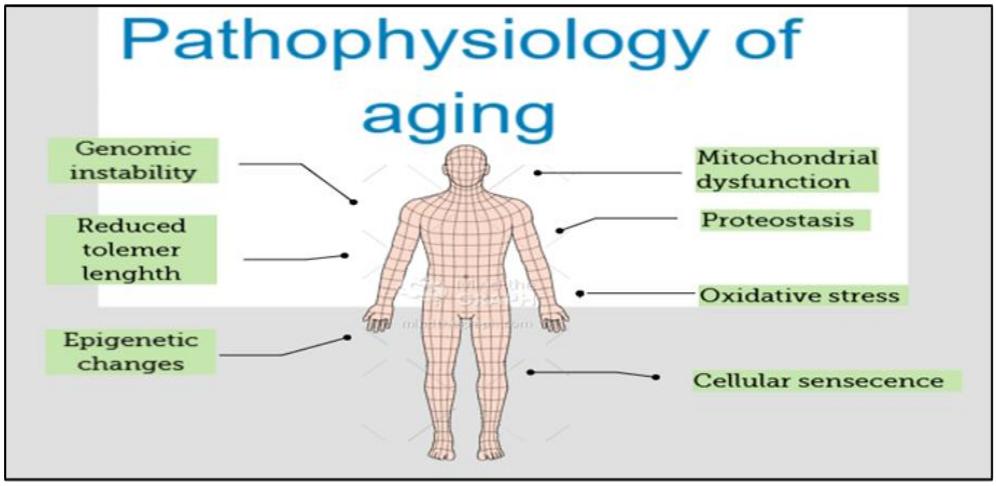

Fig 1: An abstract summarizing the pathophysiology of aging (own artwork).

Human aging causes abnormalities in the DNA repair system, which impacts the transcription pathways and expression of vital genes, ultimately resulting in cellular malfunction. According to several preclinical investigations, accelerated aging disorders are caused by impaired DNA repair ability [13] Moreover, aging is directly linked to the damage to the genome caused by old mitochondrial DNA mutations in the nuclear lamina. Research should be done to examine the effects of therapies that can stabilize the genome and restore DNA repair capacity on aging. Research has demonstrated that oxidative DNA base damage contributes to an age-related rise in point mutations in a variety of tissues, including non-replicating tissues like the brain and cerebellar neurons. [14]

2. Reduced telomere length:

It is commonly known that the aging process, which is dependent on the factors that limit cell proliferation, is regulated by shorter telomeres. When cell division causes telomeres to become abnormally short, DNA damage and cellular senescence result. Notably, telomere shortening occurs naturally in both humans and mice as they age. [15]

The oxidation of guanine, which has the lowest oxidation potential of any nucleic acid base, accelerates telomere shortening under oxidative stress. This leads to telomere length loss, dividing cells' capacity to replicate, and cellular senescence. Additionally, telomere depletion is substantially associated with ageing, biological morbidity, and death in several types of epidemiological investigations. [16, 17]

3. Epigenetic changes

Since changes in DNA methylation, histone modifications, and chromatin remodeling are associated with cell aging, chromatin modifications play a role in the aging process.[18] failure of DNA repair results in misfolded protein accumulation and aggregation, along with disruptions to epigenetic regulation. Among the aging-associated epigenetic changes that help control the aging process and age-related disorders are DNA methylation, chromatin remodeling, non-coding RNA (ncRNA) regulation, histone modification, and RNA modification[19].Age-related changes in DNA methylation have been found to occur both locally and globally in humans. Furthermore, a general loss of histones occurs in conjunction with extensive chromatin remodeling. Research into how these epigenetic pathways regulate ageing may provide targets to delay ageing.[20]

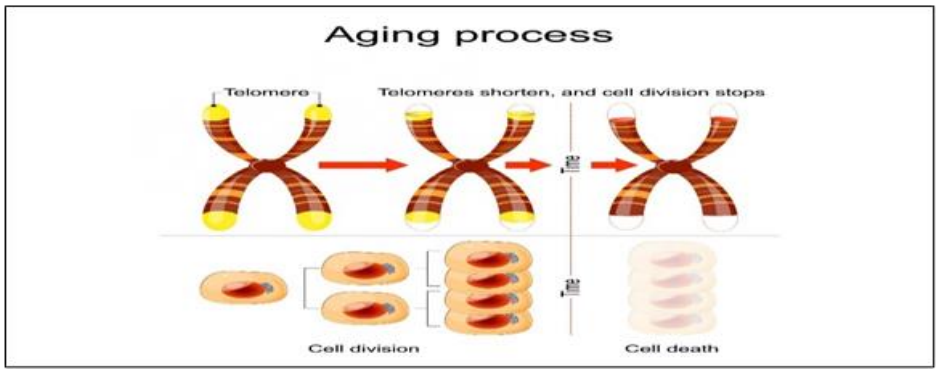

Figure 2: A diagram illustrates telomere length reduction with cell division &aging**.**

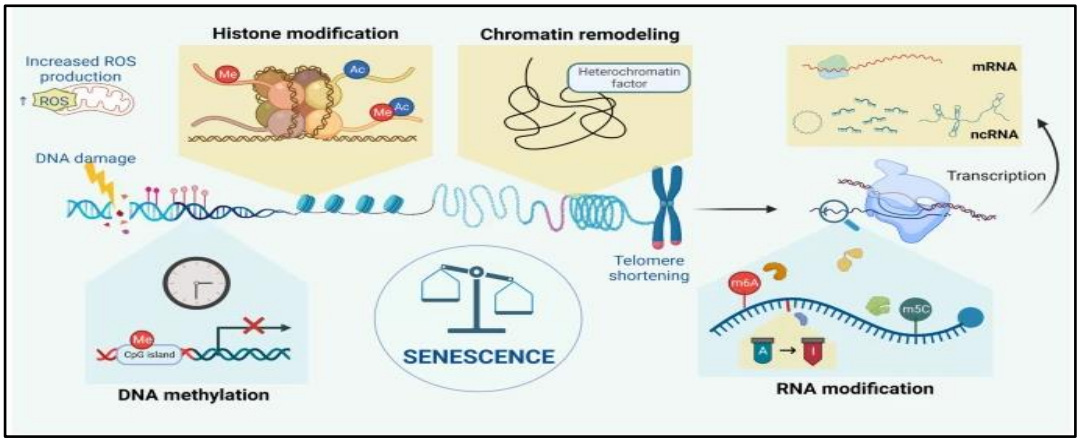

Fig (3): Changes that affect aging. Epigenetic changes that affect how DNA is expressed and proteins are made, along with increased cellular stress and senescent cells (aging cells) shown to affect various age-related diseases[19]

4. Mitochondrial dysfunction (Fig4)

Mitochondrial dysfunction is characterized by decreased mitochondrial ATP production efficiency, as indicated by a loss of mitochondrial membrane potential, increased production of reactive oxygen species (ROS), and decreased oxygen consumption[21]

Reduced muscle mass and strength are among the age-related diseases linked to lipid and protein oxidation, which changes mitochondrial metabolism and results in bioenergetic impairment. Low concentrations of ROS function as second messengers and are implicated in many cellular functions, including metabolic regulation, apoptosis, and proliferation[22]

According to the mitochondrial theory of aging, stress on mitochondria and mitochondrial DNA (mtDNA) causes aging by decreasing the amount of energy available and increasing the generation of reactive oxygen species (ROS), which damages cellular macromolecules. Most endogenous ROS are produced by mitochondrial respiration, which also produces energy by burning the calories in our meals. This leads to damage to mtDNA, phospholipids, and mitochondrial membrane proteins. This cumulative damage acts as an aging clock, and when the cumulative damage reaches a certain level, age-related disorders begin to manifest. Therefore, the mitochondrial malfunction linked to aging has been suggested as the missing link between aging and the onset of age-related diseases since it possesses all the qualities required to explain the observed hallmarks of prevalent age-related disorders[23]

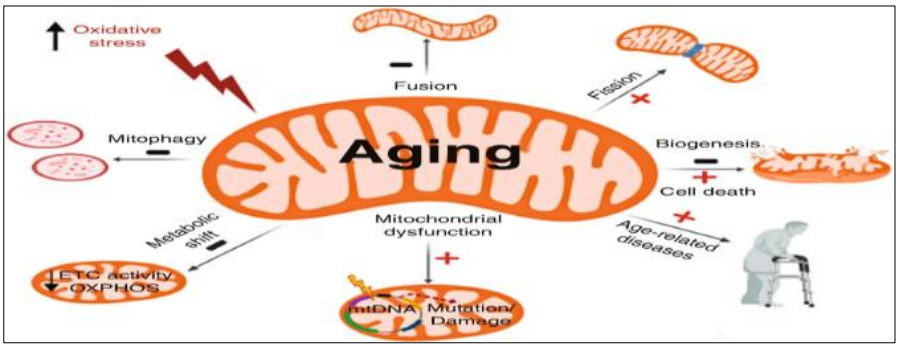

Figure 4: Mitochondrial dysfunctions associated with human aging[24].

5. Proteostasis:

Proteostasis is a tightly controlled process, and includes a variety of signaling pathways and processes linked to protein synthesis, folding, trafficcking, disaggregation, and degradation. Most aging-related illnesses and aging itself are characterized by misfolded proteins, reduced proteostasis, and the buildup of hazardous aggregates. [25]

Intercellular signaling, protein quality control, cellular senescence, regeneration, DNA damage repair, mitochondrial function, and stress responses are all regulated by proteostasis. The ability of proteases to control cellular processes is crucial for maintaining tissue homeostasis as people age. Proteases are therefore significant predictors of health span and have an impact on the developpment and course of age-related diseases. [26]

6. Cellular senescence:

Cellular senescence is a stress response mechanism that manifests as complicated morphological, chromatin-organization, and expression of specific protein biomarker modifications, in addition to replication arrest. it is a major characteristic of aging and is brought on by both internal and external harmful stimuli. The body is affected by cellular senescence in two ways. At first, tissue regeneration is impacted by a buildup of senescent cells. Second, senescent cells release a variety of inflammatory agents that cause senescence, such as severe telomere shortening, mitochondrial dysfunction, metabolic and proteostatic stress, reactive oxidative species (ROS), genomic instability, epigenetic modifications, and other processes .[27]

Cellular senescence, a defining feature of ageing brought on by cellular stress and injury, impairs tissue regeneration and repair (cellular ageing).[28]

7**. Age-Related Oxidative Stress and Oxidative Damage:**

"Oxidative stress" describes the buildup of free radicals and reactive oxygen species (ROS) in the body as a result of malfunctioning antioxidant systems. ROS have a key role in apoptosis, necrosis, migration, proliferation, and differentiation of cells. Reduced ROS levels are necessary for redox homeostasis, the control of essential transcription factors, and the preservation of numerous important physiological functions [29] The mechanism by which oxidative stress causes ageing is currently unclear. According to many studies, high ROS levels cause cellular senescence, which halts cell division in reaction to replication-related damage[30] Because of the increased oxidative damage in biological molecules, ROS, which are endogenous products of normal metabolism, have an impact on ageing. According to the "rate of living" hypothesis, in which species with higher metabolic rates have a shorter lifespan and age more rapidly, it has been proposed that energy consumption alone was the cause of ageing through the production of ROS: a faster respiration rate, associated with greater production of ROS, contributes to rapid ageing. In addition to causing oxidative stress, free radicals also reduce the activity of enzymes that scavenge free radicals, which exacerbates the negative effects of oxidative stress as people age.[31] Our biological systems contain defenses against oxidative stress, but as we age, these defenses deteriorate, which leads to an imbalance between the production and removal of ROS and increases damage caused by ROS. The primary endogenous mechanism responsible for producing ROS is oxidative phosphorylation. In this series of

mitochondrial processes, four mitochondrial enzymes process electrons from nicotinamide adenine nucleotide (NADH) and flavin adenine dinucleotide (FADH), forming adenosine triphosphate (ATP) from adenosine diphosphate (ADP). During the process, electrons are lost, forming superoxide radicals that damage macromolecules and impede tissue function .(30)

Skeletal muscle aging (Sarcopenia):

Physical limitations and the risk of immobilization disorders are linked to skeletal muscle aging, also known as sarcopenia. This condition or process is characterized by progressive structural (muscle mass loss) and functional (muscle strength) changes, and although it is typically associated with advanced ageing, it is now known to begin before the age of 60 .(32), Sarcopenia, which is more common in older populations, affects 5% to 13% of adults over 60 and 50% of people over 80. However, by age 40, muscular mass starts to decline. Therefore, both middle-aged and older persons may be impacted by sarcopenia's detrimental consequences on mortality, health care demand, and life quality .(33)

Sarcopenia prevalence varies by population; among those over 65, rates have been found to range from 10% to 50Additionally, nearly 30% of muscle mass is lost between the ages of 20 and 80. Men lose between 0.80% and 0.98% of their muscle mass annually at age 75, while women lose between 0.64% and 0.70%.(34)

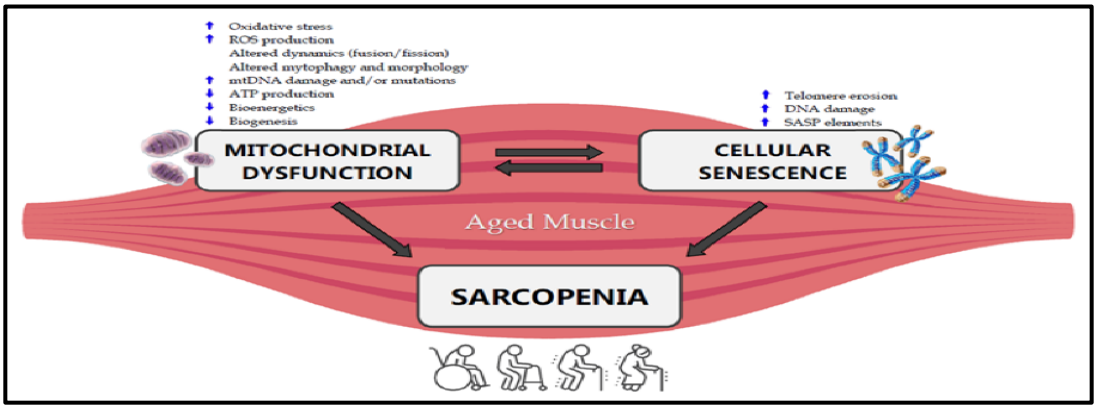

Fig (5): Interactions among cellular senescence, sarcopenia, and mitochondrial failure in aged muscle.(35)

Multiple biochemical and molecular changes in muscle structure, along with hormonal imbalances and other external stimuli, are the pathophysiology of sarcopenia.(36) Sarcopenia is thought to be characterized by the accumulation of genetic damage, including point mutations and translocations in nuclear and mitochondrial DNA, which is caused by endogenous and environmental factors. Naturally, muscle metabolism, contraction, and regeneration generate ROS. ROS is also thought to be a major contributor to aberrant proteins in skeletal muscles and DNA damage. Through alterations in gene expression and cellular senescence, damaged DNA plays a role in muscle aging(37) According to research on the telomere dynamics of human skeletal muscle, telomere length stability decreases with age. More physical activity is also typically linked to good aging and longer telomeres(38)Since autophagy's ability to remove damaged, dysfunctional mitochondria from ageing muscles is limited due to a disrupted catabolic process, which exacerbates inflammation in skeletal muscles, mitochondrial dysfunction is thought to be a characteristic of sarcopenia. It has been proposed that the mechanism that suppresses autophagy and prevents mitochondrial turnover in sarcopenic skeletal muscles is sustained activation of the mTORC1 mammalian target of rapamycin complex 1 protein signaling. It is necessary to thoroughly investigate the advantages of pharmacologically blocking this route in aged muscles in rodents (39)

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