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BIOLOGICAL AND PHYSIOLOGICAL CONCEPTS OF AGING

AZZA SAJID



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To my first teacher ..my father

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Preface

This book came to complete what was previously published, which was related to the human physiology in general without being defined by specific age group. As said by the other that physiology is the center of galaxy of all medical sciences and all other medical subjects revolve around physiology .Therefore, it was necessary to work to complete what was stated in the book "Introduction to Human Physiology" with the new book entitled "Biological and Physiological Concepts of Aging" that deals with the physiological changes accompanying aging and the effect of aging on the physiology of body systems in the elderly beside the biological bases of aging process .The book includes four chapters. The first chapter is about the concepts of aging in general, which presents the general concepts that clarify the aging processes. The second chapter deals with the causes that result in aging and discussing the different theories that explain aging processes. The third chapter shows the normal changes that occur in different body systems with age in the elderly in simple and brief presentation. Finally the last chapter is about how to improve aging, as an attempt to age in positive and healthy manner. I hope that I have presented the convenient and brief biological and physiological concepts for understanding aging.

Azza Sajid

Chapter One

General Concepts of Aging

1. Chapter One:.....General Concepts of Aging

Aging process:

Aging is a process of getting older. In humans, it represents many changes that accumulate over time including physiological, biological, physical, psychological and social changes

Although aging is one of the most important and effective risk factors of most human diseases and many people die because of age related causes, it is a natural process in individual's life as a part life cycle. It still has a positive effect on person knowledge and wisdom.

Aging process shows a progressive accumulation of changes with time that are responsible for increasing susceptibility to diseases and death. Although many changes may occur with aging, not all these changes are normally occur and some of them occur due to age related diseases, even with presence of some difficulties to differentiate between the normal changes and abnormal changes.

This book keeps focus on the normal changes that affect each body systems, or what known as a normal age. It includes the study of aging process in human beings in the fields of biology and physiology regardless to the other field that gerontologist used to study such as psychology, medicine, public health, social science, age related diseases and etc. As well as it highlights the effect of ageing on the physiology of the body system. However it is important to clarify some terms related to the age beside the normal age such as psychological age, biological age, chronological age, etc.

1.Chapter One:.....General Concepts of Aging

Normal age

Although there are differences in people ages some, changes of age are caused by internal aging process. The changes that contribute to normal age are expected and irventable such as the thickening and stiffness of the eye lens to become less able to focus in all older people, a condition called (presbyopia) .Other terms that may refer to the normal age is usual aging and senescence .

The changes that constitute the normal aging are not always distinct and clear. Certain disorders may develop as a result of changes that occur with normal ageing process these changes can be compensated to reduce and avoid the problems that they cause, by taking different healthy actions such as follow a healthy life style , eating healthy , follow up the healthy status and making regular required tests .

Biological age

Biological age refers to the biological changes that occur as individual ages. These biological changes show great differences and diversity in their appearance and time of occurring. Some people are affected by these changes sooner than others. As well as, some signs of the changes occur earlier than other signs. However, all these changes are affected by individuals' habits, lifestyle and different diseases.

1.Chapter One:.....General Concepts of Aging

Chronological age

Chronological age is term when age based only on the passage of time. It is indicated by the number of years that individual has lived. This term helps in prediction of a wide range of diseases and health problems related to age.

Psychological age

This age depends on many individual differences such as individual feeling and acting. For example when a 70 years old person takes new tasks and puts plans for futures, this person is said a psychologically young.

Healthy age

When an individual live a healthy lifestyle ,he can reduce the undesired changes of aging .This allows to maintain the physical and mental status healthy and avoid many age related disorders. This healthy age requires personal efforts such as following healthy diet, regular exercise, mental activities, etc.

1.Chapter One.....General Concepts of Aging

Human body is made up of a tremendous number of cells, about 13 trillion cells. The tissues and organs are a bunch of cells held together .Each of these hierarchy structures begins a process of aging early in the life but slightly and gradually that we cannot see .We can see whole body growing and developing.

Biological researches do not fully understand the complex interplay of factors that cause aging process. In spite that many theories have been established in order to explain aging process, will be discussed later in this book ,these theories have found many different factors that may affect aging process such as genetic , diet , exercise, illness and other factors.

In general, ageing process has a general basic concept referring to the changes that accumulate with time and ending by death but it is a different and divers feature among different living organisms. Some biological studies since 1990 have identified genes that may influence the rate at which the cells age.

At the age of 30s, aging signs begin to appear . They can be seen from different vital signs such as blood pressure, skin , bones and joints , cardiovascular system ,digestion system and nervous system . Different aging signs may appear at different points of life. Some begin early such as metabolism processes begin to decline gradually at the second decade. On the other hand hearing intensity begins to decline at late age of 50s, or even later. Gray hair, wrinkles , a slight stooped posture, some moments of forgetfulness are signs and symptoms which characterizes old age people in general.

1.Chapter One.....General Concepts of Aging

Regardless to the effect of age on each system which will be diseased in details in the next chapters, there are common signs and symptoms that occur with age these include the following:

- 1-An increase in susceptibility to infections.
- 2-Increased risk of heart stroke or hypothermic
- 3-The height decreases slightly by getting older as bones of the spine get thinner and lose some height.
- 4-Bons may break easily.
- 5-joints may change form minor stiffness to sever arthritis
- 6- The posture becomes stooped
- 7-the movement becomes slow & limited.
- 8- A decline in overall energy.
- 9- Different digestive problems and constipation.
- 10- Urinary incontinence.
- 11-Some slight slowing of thinking and weakness of memory
- 12- Decreases in reflexes and coordination and some difficulties in balance.
- 13-A decline in usual acuity and peripheral vision.
- 14-some degree of hearing loss, because the wall of ear canal gets thinner, the ear drums get thicker.

1. Chapter One.....General Concepts of Aging

15- Changes in skin and nails. Skin becomes thin and less elastic, and wrinkling .Nails grow slower.

16-Hair gets gray and less able to grow

17-Sometime weight loss occurs after 55 age in men and 65 in women due to loss of muscle tissue.

Although the great efforts that people pay to delay aging process , by healthy life style , eating healthy ,doing regular exercises sleeping enough and avoiding what may harm their life like smoking , stressful factors ,inevitable changes come with aging and people still grow older and die .

Some researchers have believed that life quality, wellbeing, level of satisfaction with life and positive health outcomes are all depend on person ability to embrace and approach to change in a positive manner. There are mental advantages by knowing how to maintain positive thinking exceeds the negativity. Challenge circumstances may improve the chance for positive changes and healing in life .After a long study on older people from both sexes scientists have concluded that the theoretical idea “life is what you make” it is true in many circumstances.

On the other hand the statement “Everything in the life is a reflection of the decision you have made” is not appropriate specifically when people challenge circumstances outside the control such as debilitating and sudden disease or chronic diseases or suffering from a great loss in their families.

1. Chapter One.....General Concepts of Aging

It is of great importance in attempt to maintain appositive mindset, striving to press forward and creating a suitable environment as much as possible, in which people can encourage healthy, helping relationship and further encouraging for older people.

Studying of aging and older people in diverse fields like social, cultural, psychological, cognition and biological aspects is the *gerontology*. It is a scientific study of process that is associated with bodily changes form middle age through later life. Understanding gerontology is of a great importance in order that people can make plans for their life to meet their requirements. Also it enables the communities to establish the public policy choices. Gerontology differs from geriatrics which is branch of medicine specialized for treatment of the age related disease.

Gerontologists are researches work in many fields such as biology, physiology, nursing, medicine psychology, physical, social science and public health. In general gerontology encompasses many fields of studies including the study of physical , mental , biological changes and social changes in old people as they age .Other field is the investigating the biological aspects of aging process which include the causes of aging process , their effects on the body system and mechanisms which are the most important aspects of this book, while other fields that gerontology deals with such as environmental gerontology , psychology and age related diseases and etc. are not included.

1.Chapter One.....General Concepts of Aging

Life expectancy

The studies showed that the average life expectancy has increased. American studies showed that male child born in 1900 might expect to live for 46 years and 48 years for female child. Today the male child may live for more than 76 and female child may live for more than 81 years. Life expectancy beyond 40 years has increased too, for example a 65 old man may be expected to live to 83 years and a woman of some age to about 85 years. Although many factors nowadays may affect woman's life style such as smoking, and exposure to more stress such as different jobs stress. However the difference in life expectancy between the man and woman has changed little.

Although the average of life expectancy has changed a lot, the maximum life span which is the oldest age the person may reach has increased little, and the chance to live to 120 years is tiny. There are several factors that may affect life expectancy such as genetic makeup, life style, healthy environment and continuous health care.

- **Genetic makeup:** It is an imperative that person who carries a genes that protect against coronary artery diseases and cancer are expected to have longer life. There are evidences that living to old age run in families.
- **Life style:** Healthy life style such as avoiding smoking, drugs and alcohol, and maintaining healthy weight and diet with regular exercises may help in increasing the life expectancy.
- **Healthy environment:** An exposure to pollutant and toxic materials may affect the life expectancy even when people have good genetic makeup.
- **Health care:** Regular checkup and follow up the healthy status may prevent certain disorders and treatment these disorders when they can be cured .This can help in increasing life expectancy.

Chapter Two

Causes of Aging

2. Chapter Two:..... Causes of Aging

Theories of Aging

Aging as an inevitable stage with continuous bodily changes, which has made the biologists study this biological stage and put many theories and hypothesis to explain aging process. Some of these hypotheses meet with each other such as “damage base theories of aging” and the “accumulation theories”. These theories' suggest that aging results from accumulation of elements which may be naturally occurring from the cell metabolism such as the accumulation of free radicals .They are byproducts of regular cellular metabolism .Other type of elements can be foreign and introduced to the body form the environment to be body from the environment. There are many explanations for these hypotheses and some explanations came overlapped such as “inflammation theory” which is involved in aging process by the effects of foreign elements or interior elements.

On the other hand, some theories particularly that follow the evolutionary causes of aging ,may conflict with the others and cancel them, for example some theories assume that aging are programmed in the genes therefore implying some kinds of evolutionary necessity in individuals mortality but the recent theories explain aging without this concept.

In general there are different theories of aging process and it is though that the most acceptable one assumed the biological aging is influenced by two main kinds of factors: **programmed factors** and **damaged related factors**.

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- 1- **Programmed factors:** These include the factors that follow a biological timetable such as the factor that regulates growth and development through childhood. This depends on the changes in the gene expression which may affect the responsible systems for repairing, maintenances and defense mechanisms'
- 2- **Damage related factors:** These include two types of factors: internal factors and external factors that may cause versions level of cumulative damage.

1- Programmed factors

Genetic aspects have been demonstrated in many studies of different species including human centenarians. Some researches demonstrated that alterations in specific genes may extend lifespan in some species such as yeast and roundworms. It has been found that some cases were associated with human longevity.

Some studies have pointed that only 5-20% of aging process has to do with our genes, while many other factors such as types of food, life style, age related diseases and problems are thought to be dangerous process that definitely affects aging of our bodies.

Genetic theories of aging propose that aging is programmed within each individual gene. Programmed cell death (apoptosis) is controlled by a biological clock via genetics information in the nucleus of the cell. The genes responsible for apoptosis provide explanation for cell death and are less applicable to an entire organism death .The increased cellular apoptosis may be correlated to aging process but it may not be considered as cause of death. Both of environmental factors and genetic mutation can influence gene expression and accelerate aging process. Recently epigenetic clock which measures biological age of cells and tissues may become useful for testing different biological aging theories.

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I. Changes in the DNA

Many researches have been done in US and Europe to study the changes in human DNA as a result of aging process .The researchers have found that epigenetic clock can predicate lifespan across different ethnicities even with presence of risk factors such as age gender weigh , smoking habit and genetic history. By using the epigenetic clock, scientists could calculate the blood and tissue age and they determined life expectancy. The changes in the DNA are represented by shortening of telomeres, DNA methylation and the variation in the gene.

- **Telomeres**

Telomeres are tiny units of DNA located at the end of each chromosome. They protect chromosomes end from deterioration. Telomeres cannot replicate completely each time the cell divides therefore they shorten over time. By growing older the telomeres get shorter and when they become very short, the cells ages and dies .So the cellular aging has been attributed to the shortening of telomeres at each cell division, therefore, the telomeres length is considered a molecular clock.

Scientists have found that some nutrients may play a great role in protecting telomeres length, hence affecting the human longevity .For example vitamin B folate plays a role in maintenance and integrity of DNA and DNA methylation which affect the length of telomeres. As well as the researchers have found that using vitamin B₁₂ supplements , vitamin D3 , zinc, iron omega 3 fatty acids and vitamin C and E may affect the length of the telomeres .This finding was also concluded by the previous study in 2009 which provided the first epidemiologic evidence that multivitamins use by women is associated with increased telomeres length These nutrients impact on the activity of **telomerase** the enzyme that adds repeats to the ends of the DNA ,thereby affecting the telomere length.

2.Chapter Two:.....Causes of Aging

Many researches have illustrated the role of telomerase in maintaining and stability of genome, preventing the unwanted activation of DNA damage pathways and regulating cellular development.

The nutrients that have beneficial effect on telomeres length include the following:

1- Vitamin D

It has been found in previous studies that women with higher level of vitamin D are having longer telomeres and those women have fewer aging related changes in the DNA and less inflammatory response. This may lead to conclude that people with higher level of vitamin D may show slower aging process comparing with people of lower level of the vitamin. Studies found that *leukocyte telomere length* (LTL) may be a predictor for aging related diseases. LTL becomes shorter with age and chronic inflammations because inflammatory response results in an increase in leukocytes turnovers . Vitamin D is considered as an inhibitor of the body inflammatory response and it reduces the inflammatory processes, leukocytes turnovers and creating positive chain reaction. This may protect the people against a variety of diseases and protect the body from the deterioration of aging.

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2- Astaxanthin

Astaxanthin is considered as a potent antioxidant with anti-inflammatory effect. It is capable to protect DNA from damage. Astaxanthin can cross the blood brain barrier and blood retinal barrier, bringing antioxidants and anti-inflammatory protection to the brain and eye. It also has a unique ability to protect the entire cell due to its physical characteristic which enables it to reside within the cell membrane.

3- Ubiquinol (CoQ10)

Ubiquinol or coenzyme Q10 is the reduced form of ubiquinon. It is used by every cell in the body and it is import for body functions. Having too little CoQ10 results in premature aging , because it recycles other antioxidants such as vitamins C and E. Its deficiency may accelerate DNA damaging and when depleted fatigue, muscle weaknesses and heart failure may develop. According to a survey in 2010 by consumer lab.com in United States, 53% of Americans were taking CoQ10 supplement.

4- krill oil (Omega 3 fats)

It has been found that omega 3 fats play a role in the activation of telomerase which affects the telomeres length. The best animal based omega 3 is krill oil which is highly resistant to oxidative damage due to containing astaxanthin.

5- Vitamin B12

Vitamin B12 is the energy vitamin in the body .It is important for many vital functions such as formation of blood cells, synthesis of DNA, formation of myelin and production of energy. It vastly improves the quality of life and protects against many life threatening diseases .It is very important to ensure that body gets adequate B12.

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6- Folate (folic acid or vitamin B9a)

Nutritional biochemistry studies have found that plasma concentration of vitamin B9 is linked to the length of telomeres in men as well as in women. It plays a role in the DNA maintenance and DNA methylation which influences the telomeres length. Deficiency of foliate may result in an increase in homocystein level which contributes in heart diseases and Alzheimer's disease. It is useful for preventing many disorders such as seizure disorders, brain atrophy and depression.

7- Magnesium

Magnesium plays a role in the replication and the repair of DNA and synthesis of RNA. Researchers have found a positive correlation between dietary magnesium and length of telomeres in women. Lack of magnesium ions causes a negative effete on genome integrity and insufficient amount of magnesium reduces the body's ability to repair damaged DNA and may cause chromosomal abnormalities.

8- polyphenols

Polyphenols are antioxidants substances available in plant. Many of polyphenols are of benefits in anti-aging process and age related diseases. Some of these potent antioxidants include:

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- Grapes: resveratrol in grapes is capable to give DNA time to repair the damage because of free radicals, due to their ability to penetrate the center of the of the cell's nucleus.
- Cocoa are potent antioxidants, therefore they are of great benefits for health. It has been found that dark organic unprocessed chocolate cause a positive influence on glucose metabolism, blood pressure and cardiovascular system.
- Green tea : Polyphenols in tea including : epigallocatechin gallate and others may protect against some types of cancers.

9- Vitamin A

Vitamin A play a role in the immune response and resistance of infectious diseases .Vitamin A deficiency results in an increase in body susceptibility to infection and inflammations which may encourage shortening of telomeres as mentioned previously.

• DNA methylation

It has been hypothesized that age has an effect on DNA methylation. Horvath*hypothesized that DNA methylation age can measure the effect of an epigenetic maintenance system.

*Marioni,R;Shah,S;McRae,A;Chen,B;Colicino,E;Harris,S;Gibson,J;Henders,A;etal.DN
AMethylation age of blood predicts all-cause mortality in later life. Genome
Biology.2015; 16(1):25.PMC4350614.PMID25633388.doi:10.1186/s13059-015-
0584-6.

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- **The variation in the gene**

It has been found that FOXO3A is much more in people who live for 100 years and more, therefore its thought that Foxo3A has a positive effect on the life expectancy. FOXO3A affects the sirtuin family of genes which in turn suppress mTOR protein.

MTOR protein inhibits autophagy, which is the process by which the cells digest their own components .According to many previous studies it has been found that autophagy has a role in the aging process. It was concluded by a previous study * applied on flies that disruption of autophagy shortens the life span , while enhancement autophagy increase life span significantly. Dysfunction of autophagy has been correlated to neurodegenerative disorders. Another study** has concluded that autophagy decline with age. Maintenance of autophagy through genetic manipulation may improve the cell ability to handle protein damage resulting in a decrease in the level of damaged proteins and an improvement in the functions of organs. ***

*Johnson S C;Rabinovitch P,S and Kaeberlein MMTOR is a key modulator of aging and age related disease. Nature. 2013;493(7432):338-45.Bibcode:2013Nature.493..338J.doi:10.1038/nature11861.

**Morgunova GV, Klebanov AA, Khokhlov AN. Autophagy—the way to death or immortality? Activators and inhibitors of autophagy as possible modulators of the aging process. Aging: exploring a complex phenomenon/ed. Sh. I. Ahmad. Boca Raton: Taylor & Francis. 2018:475-85.

***Zhang C. and Cuervo A M. Nat. Med. Restoration of chaperon-mediated autophagy in aging liver improves cellular maintenance and hepatic function. 2008 Sep; 14(9):959-965.PMCID:PMC2722716.PMID:18690243.doi:10.1038/nm.1851.

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II. Metabolism & Caloric Restriction(CR)

The old physiological studies have pointed that there are correlations among metabolic rate, body size and longevity (life span) .It has been found that long lived species are bigger and spend less calories per gram of body mass than smaller short lived species. In fact the animal is born with a limited quantity of materials, potential energy and physiological ability, hence it has been suggested that animal will grow faster when biochemical activities and metabolic rate run faster .It means that aging may result from the velocity at which the life is active. The scientists propose that caloric restriction (CR) has a role in the aging process and it works to delay the metabolic rate in conformity with energy consumption, thereby lengthen the life span in many species.

III. Growth hormone/ Insulin – like Growth Factor I signaling pathway

A decrease in growth hormone / insulin like growth factor I signaling pathway has been found to be associated with long lifespan in various species. The mechanism by which the lifespan increases is not clear but a previous study was applied on various strains of mouse has concluded that decreased GH / IGF1 signaling may affect positively the insulin sensitivity and stress resistance resulting in protection against carcinogenesis.

2.Chapter Two:..... Causes of Aging

IV. The Evolutionary Cases

Some theories assume that aging process is programmed in the genes, and that lifespan is naturally selected. The genetic effect on the aging is called the antagonistic pleiotropy effect.

The individual is disposable carrier to replicate the information in the genes. As long as the gene survive (replicated in offspring before individual death), the individual survival is not that serious. This leads to what is known (disposable soma concept).The main concept is that each evolutionary adaptation is expensive because the resources (energy ,time and materials) are used by the genes just for a specific function, therefore they will not be available for another function. It is impossible to maximize two different functions at the same time ,for example in case of reproduction and survival, the genes enable the reproductive ability at youth at the expense of life expectancy in old age. The most important criterion for gene to be naturally selected is that its individual should have long lifespan to produce numerous offsprings. The genes of individuals that do not age and survive long would be naturally selected. However aging process and mortality are controlled by two factors *internal factors* and *external factor* (diseases and accidents), as shown in figure 1. In spite of the fact that gene can make its carrier stronger and more resistant it can never exclude the effects of external (factors causing death).

2.Chapter Two:.....Causes of Aging

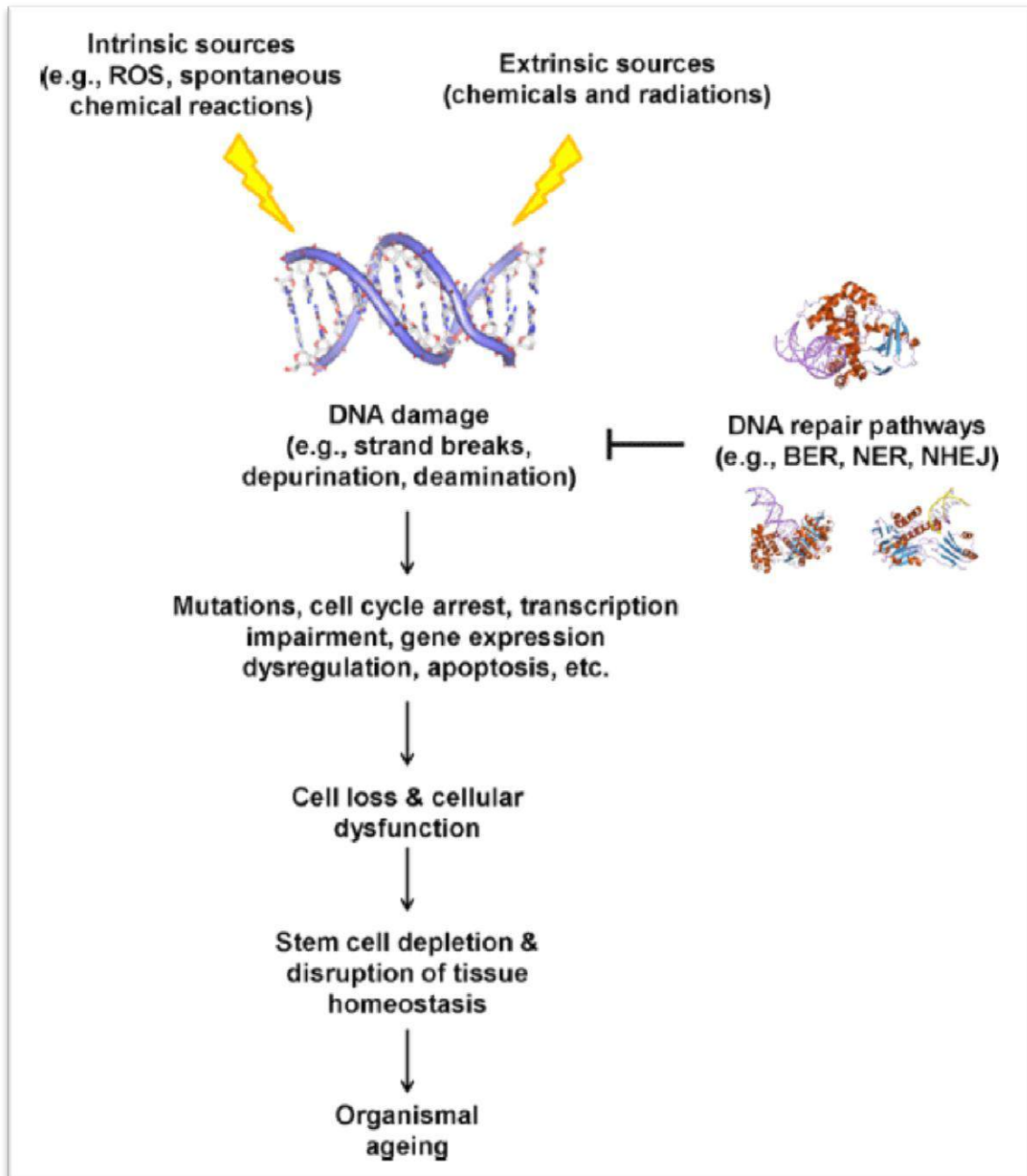


Figure 1: The role of both internal factors and external factors to induce ageing. (Freitas AA, de Magalhães JP. A review and appraisal of the DNA damage theory of ageing. *Mutat Res.* 2011;728(1-2):12-22. doi:10.1016/j.mrrev.2011.05.001)

2.Chapter Two:.....Causes of Aging

V. The Reproductive –Cell Cycle Theory

The reproductive cell cycle theory assumes that aging process is managed and controlled by reproductive hormones. These reproductive hormones act as an antagonistic pleiotropic way through cell cycle signaling to move up the growth and make the individual capable to reproduce during youth stage. Later these hormones become dysregulated and uncontrolled in a way that leads to aging with useless attempt to sustain reproductive ability. The loss of follicles during menopause and as well Leydig and Sertoli cells during andropause resulting from endocrine impairment leads to abnormal cell cycle signaling and cell death finally. Furthermore reproductive hormones can also regulate cellular functions and metabolism. Therefore, the impairment in reproductive hormones can definitely result in abnormal cellular function and deteriorated metabolism.

VI. Autoimmune Process

Autoimmune process is considered to be of a great role in aging process and age related diseases such as atrophic gastritis, Hashimoto thyroiditis (a chronic lymphocytic thyroiditis in which antibodies targeted against thyroid tissue leading to chronic inflammation) and Alzheimer. Autoimmune process is characterized by an increase in auto-antibodies that are directed against healthy body's cells and tissues.

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2- Damage Causing Factors

Damage theory is the theory that based on the concept that damage is caused by either normal toxic byproducts of metabolism and cellular function or by inefficient repair. These different forms of damages accumulate throughout the life resulting in aging. (Holliday, 2004*; Kirkwood, 2005 **).

Functional failure of the body systems can be result from slow build up and delay in the repairing of the damage .Hence this damage can cause failure of vital organs such as heart, kidney or even failure of whole body. It has been found in a previous study that the errors in DNA repair influence the information current in the cells. An old study (Orgel,1973)*** assumed that the error in the transcription process form DNA results in an error in protein synthesis and produces damaged proteins. This in turn, leads to further error in transcription process .The frequent wrong events kill the cell and cause aging process. Damaged portions accumulate over the time leading to loss their ability to perform different functions such as losing the catalytic activity with age. These events result in different functional abnormalities and cellular dysfunction which definitely create further damage. In more recent studies it has been approved that these events are more likely to be involved in age related diseases.

*Holliday,R.The multiple and irreversible causes of aging.*J Gerontol A Biol Sci Med Sci* 2004; 59(6):B568-572.

**Kirkwood T.B. Understanding the odd science of aging.*Cell* .2005;120(:4)437-447.

***Orgel L.E. Aging the clones of mammalian cells. *Nature*.1973;243(5408):441-445.

2.Chapter Two:..... Causes of Aging

I. DNA damage theory

Many hypotheses assume that *DNA damage* is the common cause of aging process and age related diseases, such as cancer.

DNA damage results in cessation of cell division hence no more regeneration may occur. It has been suggested that only specific kind of change in DNA play a crucial role in aging process giving an explanation why mutations (changes in DNA sequins) in some DNA repair genes influence aging process whereas the other do not. An evidence by Hoeijmarkers , 2009 * proposed that DNA damage that involves in mutation and chromosomal aberrations lead to increase the risk of cancer, whereas DNA that play a part in transcription contribute to aging process by affecting the cellular aging and cell signaling. Another hypothesis by Trifunovic ,*et al* ,2004 ** assumes that mitochondrial DNA polymerase may accelerate aging phenotype in mice, and mitochondrial DNA may play a role in the age related diseases and aging process. Finally this theory assumes that genetic damage is considered to be the main cause of aging process and that DNA damage is done in majority by the effect of reactive oxygen species (ROS) .

*Hoeijmarkers ,J.H. DNA damage ,aging and cancer .*N Engl J Med*.2009; 361(15):1475-1485.

**TrifunovicA.,Wredenberg,A.,Falkenberg,M.,Spelbrink,J.N,Rovio,A.,T.,Bruder,C.,E.,B ohloly,Y.m.,Gildlof,A.,Wibom,R.,et al.Premature aging in mice expressing defective mitochondrial DNA polymerase .*Nature*.2004; 429(6990):417-423.

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II. Accumulation theory of aging

Accumulation theory of aging proposes that there is overall decline in body function and system. This decline is caused by an accumulation of different elements which may be external elements (foreign) brought to the body from the environment, for example continuous exposure to specific material. Accumulation of this material with time creates hazardous effect on the body and resulting in a degeneration which may contribute to aging related diseases such as cancer.

The other factors are internal factors which are naturally produced in the body as a result of cellular metabolism such as accumulation of waste. Accumulation of waste products in the cells may confuse and obstruct the normal metabolic process for example what is called lipofuscin , the waste product formed by complicated reactions in the cell and associates between fats and proteins . The waste product accumulates with time forming particles which grow in size with aging .

Another example of the naturally produced materials in the body is the formation of free radical. Accumulation of free radical with time has an important role in aging process according to free radical theory of aging.

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III. Free radical theory of aging : -

An accumulation of free radicals in the cells and DNA over time results in cellular dysfunction and aging , according to the free radical theory of aging which was proposed by Herman in 1956 * .

Free radicals are atoms or molecules characterized by having unpaired of electrons, hence these molecules are unstable and highly reactive. They attack the neighboring molecules to take or (give) an electron to be stable in process called oxidation. The target molecules are cellular compartments including proteins, lipids ,DNA and cell membrane. These free radicals alter the structures of the affected molecules. On the other hand, antioxidants accept or donate an electron from the free radicals to make them stable and stop their damaging effect. These antioxidants are characterized by their ability to stay stable even when they donate or take an electron and by their scavenging activity against free radicals. This scavenging capability differs and varies among the different kinds of antioxidants.

Oxidation process initiates a chain of chemical reactions by damaging the cellular structures,such as DNA, and their functional abilities. Over time the oxidative damage accumulates and contributes to aging process and many age related deteriorations .

* Herman D.Aging: A theory based on free radical and radiation chemistry. J Gerontol.1956;11(3):298-300.

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There are many types of free radicals and the most related to the biological process are those which derived from oxygen: the Reactive Oxygen Species (ROS). These ROS include superoxide anion , peroxide and hydro radicals . ROS are produced in vivo within the mitochondria during electron transport chain. They are also produced as intermediate products in different enzymatic reactions and by different physiological processes such as:

- Phagocytic activity of white blood cells, specifically neutrophils. Neutrophils generate ROS during phagocytic activity in order to kill the invading pathogens as a host defense mechanism.
- When the cells are exposed to abnormal conditions -such as hypoxia or hperoxia-produce ROS. Some drugs have the ability to induce the cells to produce ROS due to their oxidizing effect.
- An exposure to radiation may induce the biological systems to produce ROS.

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In general, generation of ROS increases under some specific conditions such as inflammatory processes, stress, illness and aging process. As well as some external factors such as an exposure to hazardous environmental factors, including pollution, toxic metals, industrial chemicals and cigarette smoking may increase the chance to produce more free radicals as illustrated by figure 2.



Figure 2: The external sources of free radical.

(Wojtunik-Kulesza KA, Oniszczyk A, Oniszczyk T, Waksmundzka-Hajnos M. The influence of common free radicals and antioxidants on development of Alzheimer's Disease. *Biomed Pharmacother.* 2016;78:39-49. doi:10.1016/j.biopha.2015.12.024)

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Although that free radicals production may be required and desirable in some biological processes due to their effective roles in these process such as defense mechanism against the pathogens and other functions, their production must be under control and in balance with antioxidant system. The imbalance between generation and elimination of ROS create certain pathological effect on cell physiology .This pathological condition is called oxidative stress which may result in many health problems and degenerative disease such as heart disease , hypertension , arthritis , Parkinson disease , al Alzheimer's disease ,cataract and etc. As well as it contribute to acceleration of aging process hence ROS are considered as damaging agents in living organisms.

The most known toxic effete of free radicals is their damaging to the cellular compartments e.g., plasma membrane, mitochondria and endomembranous system. The damage includes a process called (lipid peroxidation)and the target material of this process is the unsaturated fatty acids which present in the membrane phospholipid .Lipid peroxidation of cellular membranes can cause different effete including the following:

- An increase in the rigidity of the membrane.
- A decrease in the activity of membrane bound enzymes, leading to change in sodium pump.
- An alteration in the activity of membrane receptors
- Changes in membrane permeability.

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Another plausible effect of free radicals is that they cause a cross linking of atomic structures, when DNA becomes cross-linked, a wide range of effects related to aging process and age related diseases may occur. When cross linking takes place between lipid and proteins many changes of appearances such as wrinkles may occur.

However the effect of oxidative stress depends on its classification which is based upon its intensity .Therefore, oxidation stress may be basal oxidative stress when its intensity low, intermediate oxidative stress and high oxidative stress for the high intense oxidative stress.

Harman's hypothesis (free radicals theory of aging) was modified later to include the role of mitochondria in aging process. which proposed that free radicals produced in mitochondria result in damage to the macromolecular such as lipid, protein and mitochondrial DNA .This damage result in mutations which intern lead to increase ROS generation and accumulation of free radical within the cells, the life span is determined by the oxidative damage that caused by these free radicals to the mitochondrial DNA.

IV. Wear & Tear theory : of aging

This theory suggests that body parts such as cells and organs wear out from sustain work by aging. This happens because of some internal and external factors that lead to accumulate the obstacles that suppress the capacity for repairing. As a result the cells lose their ability to regenerate and become chemically and physically fatigue. Some of these factors include chemicals in the air , unhealthy food , smoke ,viruses , trauma, stressful conditions and cross – linkage may be involved.

Stressful conditions

Stressful conditions may induce releasing of various stress hormones. These hormones are released under stress and result in different effects and problems including an increase in heart rate and blood pressure as well as diabetes mellitus may develop. When the stressful conditions stay long, cortisol hormone is released to lessen these effects, but it creates many other health problems specially when it is chronically increased. This may affect the long term memory by affecting the hippocampus in the brain .Stressful conditions play a role in accelerating aging process and initiating many age related problems. They lead to accumulate of belly fat causing inflammation and insulin resistance.

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Unhealthily life style

Many factors related to life style such as exercise, smoking, alcohol and caloric restriction may affect the life span by delay or even prevent some age related diseases .Getting enough amount of sleep is one of the life style factors that may impact on the aging process and mortality. It has been found that amount of sleep less than five hours per day may create many age related problems and increase the risk of death because of cardiovascular diseases.

V. General imbalance theory

General imbalance theory of aging proposes that all body systems, such as ending all system, cardiovascular system nervous system, immune system and respiratory system show gradual decline and even failure to do their normal functions .The rate of the failure varies from system to another.

The most significant factor in aging process

After reviewing all theories and hypotheses related to aging, the most debatable question is about the influential factor in this regard. It is unclear what the actual spectrum of each affecting factor in aging is, furthermore the percentage of impact that each would create cannot be determined.

In fact the hypothesis based on synergistic interaction among the causes of aging and that the most important one may be influenced by relativistic effects of the others provide a plausible

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explanation. In other world no one of these causes can work independently. Whereas that damaging accumulation idea appears to be preferable by many researches, it has unclear explanation why a balance between damaging accumulation and repairing cannot be regulated and maintained over time in an organism. Other inexplicable thing is why the oxidative damaging species such as superoxide anions are not removed by superoxide dismutase? And why the brain which is a highly active organ contain low antioxidant protection. Therefore, the damaging effect of free radicals is accepted by some researchers and not accepted by the others.

Chapter Three

Effect of Aging on the Physiology of Body Systems

3.Chapter Three:.....Effect of Aging on the Physiology of Body Systems

Aging results in many physiological phenomena on the cells and tissue level. These physiological phenomena are generally represented by a decrease in the cells count, deterioration in the proteins of the tissues, atrophy of the cells and tissues, a decrease in the metabolic activity and rate, a decrease in the body fluids as well as deterioration the metabolism of some ions.

All the changes that occur due to aging processes definitely affect the functions of all body systems even though the effect may occur at a different rate .Some systems begin aging process at early age ,on the other hand ,other systems may age later in the life. Although certain changes always take place with age, they take place at different rates and to different extents.

This chapter sheds light on the effect aging process on the functions of each body system. There are many terms that describe the changes due to the aging, these terms include the following:

1. Atrophy

In atrophy cells shrink, if enough cells decrease in size, the entire organ atrophies. This change occurs after normal age in any tissue and organ such as breast and ovaries .Bone becomes thinner and more likely to break with minor trauma. The cause of atrophy is unknown but it is likely to due to reduce use, decreased workload, decreased blood supply or nutrition to the cell and reduced stimulation by nerves and hormones.

2. Hypertrophy

This is when cells enlarge. It is caused by an increase of proteins in the cell membrane and structures but not an increase in the quantity of the fluids. With age when some cells atrophy, others may hypertrophy to make up the reduction of cell mass.

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3. Hyperplasia

The number of cells increases .This is due to an increase in the cell division rate. Hyperplasia occurs to compensate the reduction of the cells .It allows some tissues and organ to enlarge such as skin, liver and bone marrow. For example liver can replace up to 70% of its structure within two weeks after an injury.

4. Dysplasia

The size, shape and organization of the cells turn abnormal. This also may be called atypical hyperplasia .Dysplasia is common in the cells of cervix and the lining of the respiratory tract.

5. Neoplasia

This means formation of tumor either malignant or benign. Neoplastic cells divide and reproduce rapidly and they may have unusual shapes therefore abnormal functions.

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1. Effect of Aging on Respiratory System

With age, respiratory system undergoes various anatomical and physiological changes resulting in different alterations in whole system. However these changes occur at different rate.

Thoracic cage undergoes changes due to the deformities that occur in the chest walls and thoracic spine . As a result to these changes, pulmonary volumes and compliance decrease. As well as stiffness of the thoracic cage that result from calcification of the rib cage and age related deformities such as osteoporosis reduce the expansibility of the thoracic cage during inspiration.

Respiratory muscles including the diaphragm and internal intercostal muscles which play the major role during inspiration , become weak with age , according to the indicators of the inspiratory muscles strength these indicators include the following:

- **Inspiratory Pressure (MIP)** is an indicator of inspiratory muscle strength, It may also determine the vital capacity of the lung. A decreased MIP lead to insufficient ventilation and inability to clear the secretion of airways .
- **Trans-diaphragmatic Presume (TDP)** is another indicator of the inspiratory muscles strength that declines in about 25% in older healthy subjects of age 65-75 years when compared to the young healthy adults .
- **Maximum Voluntary Ventilation (MVV)**, this indicator is also reduced with age due to inability to expand the chest to its maximum expansion. This inability is caused by reduced diaphragmatic strength and age related muscle trophy.

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The significant decline in the strength of the chest muscles and respiratory muscles make elderly more vulnerable to muscle fatigue and respiratory failure when they expose to ventilatory load on the respiratory system .Moreover these weak muscles may decrease the effective cough which is required to clean the airway passage.

Another factor that makes pulmonary compliance decrease is the reduced alveolar elasticity and elastic recoil of the lung. Elastic fibers around the alveolar duct are lost leading to premature closing of small airways during normal expiration. The reduced thoracic compliance makes the expiration of the air from the lung difficult. Therefore, residual volume (RV) and functional residual capacity (FRC) are increased, while vital capacity (VC) is reduced. Most cross sectional studies showed a linear decline in the forced expiratory volume at the first second of expiration (FEV1) with age. The rate of decline at age 35-40 years is about 25-30 ml per year , while it may reach to 60 ml per year after age 70 years .

The different categories of lung functions such as static lung volumes , dynamic flow rate and gas exchange across the respiratory membrane undergo variable changes with age . In general lung functions remain stable between 20 to 35 years old and begin to decline after that age. In fact it is difficult to predicate a normal range of change in the functions for elderly because of the variable physiological measurements. It has been proved that tidal volume (TV) changes with age , and in order to keep the Minute respiratory ventilation MRV regulated and controlled, the respiratory rate changes . As well as both of Inspiration Reserve Volume (IRV) and Expiratory Reserve Volume (ERV) decrease, hence vital capacity decreases.

The premature closing of airways results in mismatching in ventilation –perfusion ratio (AV/Q).The decrease in the number of functional pulmonary alveoli and pulmonary capillaries that surround the these alveoli leads to decrease in the area of gas exchange : the respiration membrane and hence affecting the oxygen (O₂) and carbon

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dioxide (CO₂) exchange (reduced diffusing capacity) and transport of gases.

There is a significant decline in the ventilatory response to high CO₂ tension or low O₂ tension . It has been found about 50% reduction in the response to hypoxia and 40% reduction in the response to hypercarnia. This reduced response is due to the decline in the efferent neural output to respiratory muscles during hypoxia or hypercarnia of the elderly. Other effect of aging in respiratory system is manifested by an increased susceptibility to infection and bronchitis. This is because of an increase in the accumulation of mucous which become more viscous and decreased number of cilia which make the mucus difficult to remove, in addition to the decreased activity and efficiency of the cellular defense against invading microorganisms and foreign bodies .

Chronic obstructive pulmonary disease (COPD) is one of the most common respiration diseases in elderly and it considered to be the major cause of respiratory failure and intensive care admission. However, the age is not a risk factor of respiratory failure but elderly have an elevated risk of death because of acute respiratory failure and intensive chronic respiratory failure. Overall respiratory changes are illustrated in figure 3.

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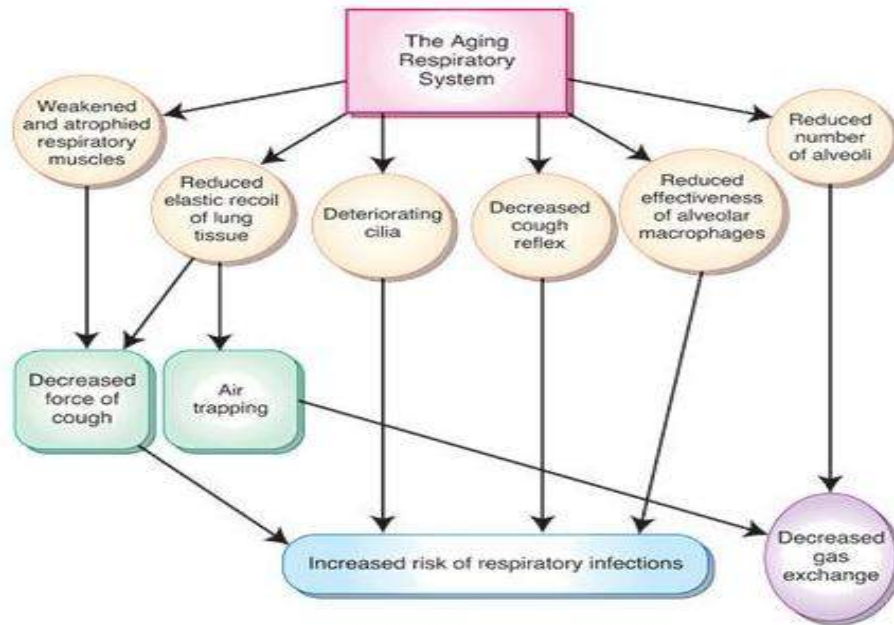


Figure 3: Effect of Aging on Respiratory system. Modified from (Scanlon VC, Sanders T. Essentials of Anatomy and Physiology. F.A. DAVIS COMPANY. 2011; 672 p).

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2. Effect of Aging on Nervous System

In general, there are different changes in nervous system with age. These changes are quite variable among old people, some people may undergo many changes in the nerves and brain, while others have few changes.

I. Sensory neurons

The number of sensory neurons are reduced with age; therefore, sensory functions decline and processing of central nervous system (CNS) decreases. Old people are less conscious to something that touch their skin due to the decrease in the number of Meissner corpuscles and Pacinian corpuscles . Furthermore they show a decrease in sense of two points discrimination and the ability to identify the objects by touch.

Other deteriorations in neural functions which are related to age are the balance and coordination of the movements because of the decrease in the sense of limbs position . Furthermore the functions of Golgi tendon organ and muscle spindle decrease with age .This leads to reduce the information on the position and further decrease in the control of posture and movements. It has been found about 35% of 70 years old peoples and 80% above that age suffer from gait abnormalities and limitation in movements. These changes in turn result in losing of personal independence and decrease quality of the life besides presence of more difficulties with dual task such as stop walking while talking.

Old people are more likely to suffer from high blood pressure, dehydration , urinary incontinence and bowel incontinence. These problems occur due to decreased functions of sensory neurons that detect blood pressure changing, sensation of thirst , the amount of urine in the bladder and amount of feces in the rectum .

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II. Motor neurons

Motor neurons are also reduced in number with age , for example the lower motor neurons in the lumber region are reduced to its half number by age 60 years . The maiming neurons may compensate for some functions that may lead to rapid fatigue.

III. Reflexes

As people age, the reflexes become slower , because the generation , conduction of action potential as well as synaptic function become slow. The numbers of neurotransmitters and receptors decline. All these factors make old people lose their ability to response quickly and accurately to the changes in the conditions.

IV. Brain

The brain deceases in weight and size with age because of breakdown and losing of some neurons. Furthermore the remaining neurons undergo many structural changes including increased rigidity of the plasma membrane, irregular structure of endoplasmic reticulum and amyloid plaques that arise in the synapses .

These structural changes make the neurons less functional ability. The functional changes include conscious sense, memory, movement and sleep. Short term memory is affected while long term memory is unaffected. These changes appear to be more rapidly deteriorated after age 70 years. Mental functions such as vocabularies, ability to learn new language, ability to recall words are decrease after age 70 years old.

Thinking activates such as intelligence, solving the problems declines with age. However, these changes depend on people's background education, health status, and life style.

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Sleep disorders is another change that old people suffer from because sleep may be affected by many factors such as digestion problems, capacity of urinary bladder , sleep apnea, pain and movement difficulties .

Special Sense in age

All of the senses such as hearing, vision , taste , smell and touch change with age . Their sensitivities decline and become less sharp. In fact hearing and vision are the most influenced by aging. The changes that occur in these senses lead to limit different activities of life and may create problems in communication.

One of the most important changes is represented by an increase in the amount of stimulation, which is required to initiate the threshold (the beginning of sense).This stimulation becomes greater than that required to initiate the sense doing youth.

I. Hearing

The internal structures of the ear show several changes; therefore, their functions decline. It is obvious that old people lose their ability to pick up the sounds sharply and differentiate between certain sounds. The number of hair cells in the saccule utricle and ampullae decreases as well as the number of otoliths .These changes make old people less sensitive to gravity and undergo vertigo, that result in a decreased ability to maintain and balance while changing the positions. A case that definitely increases the risk of fall. Tinnitus is common problem among old peopled due to accumulation of wax or damaging of some internal structures of the ear. Moreover old people may suffer from presbycusis that affect both ears.

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II. Vision

Many age related changes in the eye such as decreased sensitivity of cornea, decreased size of the pupils and slow response to darkness or light, make the vision highly affected in old people.

The lens becomes yellowed and less flexible. The muscles of the eye become weak; therefore, they lack their ability to complete rotation and activity to interact and communicate with the others. The eye are less able to tolerate glare and even less able to adapt to bright light. Old people may have problem in distinguishing certain colors such as green or blue, red or orange.

In some cases, gel like substances inside the eye begin to decrease, leading to form fine particles, which are known as floaters (the fine particles in the field of vision) . This condition may create a problem in the vision when it develops suddenly or increases rapidly.

Aging eye may not produce enough tears which result in a dry eye .Dry eye is more susceptible to infection and inflammation specifically if not treated. Artificial rears or using eye droops may help in this case. There are common disorders in old age people that results in vision changes such as presbyopia , cataracts ,glaucoma , retinopathy and macular degeneration.

1. Presbyopia : is the most common condition among old people which is difficult to focus the eye on close up objects
2. Cataract : cloudy of the eye lens
3. Glaucoma : is an elevated fluid pressure in the eye.
4. Retinopathy : is a disease in the retina, which may result from high blood pressure or diabetes mellitus
5. Macular degeneration : is a disease in the macula

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III. Taste and Smell

The taste and smell senses work together and most taste connect with odors. They play important roles in the enjoyment of food as well as in the safety, by detecting dangerous materials such as spoil food, gases and others . The sensitivity of the five tastes sweet, salty sour , bitter and other flavors usually decrease after age 60 years . The number of taste buds declines with age and the remaining taste buds get smaller.

Old people may suffer from dry mouth because salivary glands produce less saliva. Smell sense declines after age 70 years due to losing of nerve endings and decrease in production of mucus in the nose . Mucus makes odor stay longer to be detected by the nerve endings.

IV. Touch

Sense of touch reduces with age because of decreased blood supply to the nerve endings or to spinal cord which transmit signals. Other probable reason is the decrease in blood flow to the brain where signals are interpreted .

Deficiency of certain nutrients as well as some age related diseases such as diabetes mellitus may cause changes in sensation. These changes vary depending on the cause and the source. The decline in the sensitivity of temperature increases the risk of burns and hypothermia (low body temperature). As well as decreased sensitivity to detect the objects , the change in touch and perceive lead to increase the risk of injuries .Another serious case is that old people are at risk of fall down because of decreased ability to perceive the exact position of the body on the floor.

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3. Effect of aging on integumentary system

The integumentary system is considered the largest system in the body. It composed of skin and appendages such as sebaceous glands, sweat glands, nail and hair. It acts as a protective barrier against environment as well as a sensory organ. Skin changes are one of the most visible markers of aging. These include wrinkles, sagging skin and whitening of hair.

The skin is composed of three layers: the layer that contains skin cells ,pigments and protein(the epidermis);the middle layer that contains nerves, blood vessels and fat(the subcutaneous layer)and the last layer contains collagen fibers ,connective tissue and elastin fibers. These elements give the skin strength, elasticity and support. Therefore any effect on the skin will result in changes in these functions. Sensation of touch, pressure and pain change with age .Elderly become less able to regulate fluid and electrolytes balance,less able to control body temperature and less protected against environmental factors.

The changes of integumentary system with age are both intrinsic and extrinsic. The intrinsic changes of age are caused by internal factors (physiological processes) such as decreased synthesis of collagen and elastin in the dermis. On the other hand, the extrinsic changes of age are caused by external factors such as an exposure to UV, cigarrete smoking , pollution and etc.... These factors have the most negative effect on the skin.

The changes in the skin are demonstrated in the reduced mitosis in the stratum basal which lead to a thin epidermis. Elasticity and strength of the skin reduced with age leading to what known as elastosis due to decrease in connective tissues. The dermis became less able to regenerate leading to slower wounds healing. Skin ,in particular sun exposed area such as face and hands begin to show the first visible marks of aging.

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Wrinkling occurs due to decreased production of collagen and elastin in the dermis and muscles lying under the skin become weak. Subcutaneous fat layer becomes thin also with reduced insulation which elevates the risk of skin injury and reduces ability to maintain body temperature. Furthermore, sweat glands become less active in production sweat, which increase the intolerance to extreme heat. Sebaceous glands, secrete less oil reaching to minimal decrease after age 80 in man .In woman this function gradually decrease after menopause resulting in dryness.

Other structures in the skin such as melanocytes (pigments containing cells)decrease with age ,therefore aging skin appear pale and thin with pigmented spots. Activity of dendritic cells decreases resulting in deduced immunity. The thin and fragile skin increase the risk of injury .Moreover skin repairs itself slowly and healing of wounds is about 4 times slower because of deceased immunity and blood vessels changes.

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4-Effect of Aging on the urinary system

With age, the kidneys decrease in size. this decrease in size is due to changes in the blood vessels of the kidney. The afferent and efferent arterioles undergo changes too. They become twisted, therefore the amount of blood flow to the kidneys declines.

The structures of some nephrons and collecting duct become irregular, shorter and thicker. These nephrons become nonfunctioning due to the reduction in the capacity of secretion and absorption. The ability to produce concentrated urine decreases which may lead to dehydration. As well as the ability to remove urea , uric acid ,creatinine and other waste products from the blood decrease. The responsiveness to some hormones such as antidiuretic hormone (ADH)and aldosterone declines besides the decline in the secretion of rennin.

Kidneys show less ability to get involved in vitamin D synthesis, which may be a cause in development of Ca^{2+} deficiency and osteoporosis.

Old people cannot control the urination very well and the urination times increase. In fact there are many changes that may lead to uncontrolled urination such as a decrease in maximum urine volume which can be contained in the urinary bladder .The muscles of the bladder become weak and less able to clear the bladder completely, as well as they may contract even when there no urination, and finally urinary sphincter loses its ability to close tightly so it cannot prevent leakage. Figure 4 summarizes several structural, physiological and clinical changes in the kidneys that develop due to aging.

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In old men , the prostate gland may enlarge , some time to a point that it can impede the passage of urine . Urine retention may develop in men with age leading to what known as urination disorder. The man becomes unable to urine even when he has full bladder. In women, the decrease in estrogen level may result in some changes such as shortness of urethra.

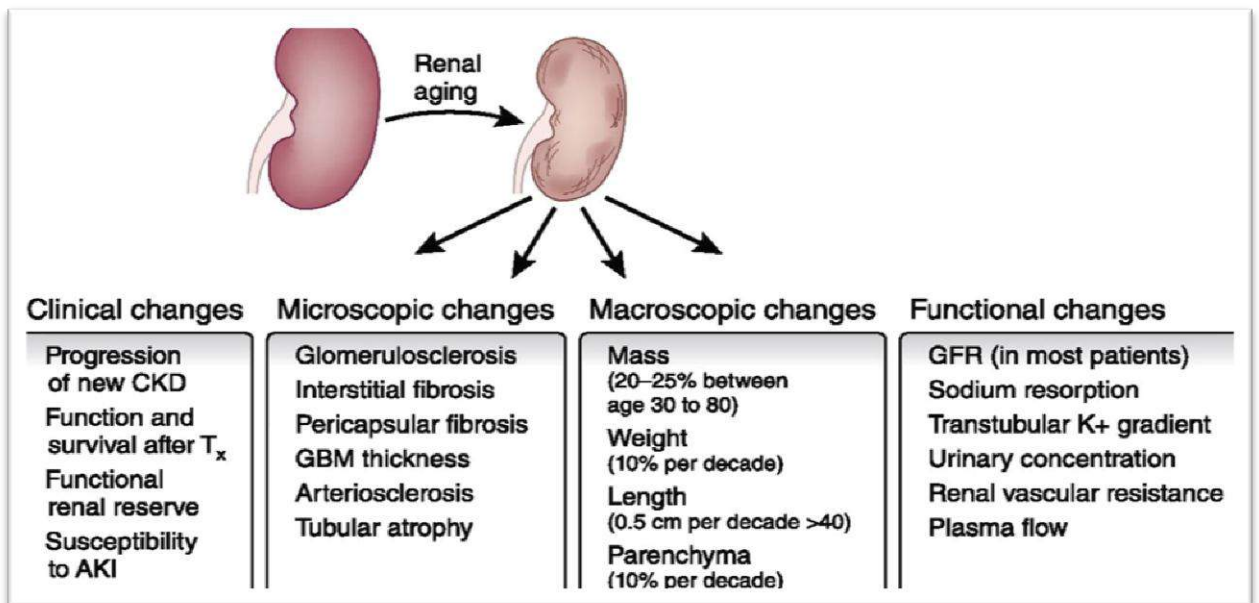


Figure 4: Structural ,physiological and clinical changes in the kidney that develop due to aging. (O'Sullivan ED, Hughes J, Ferenbach DA. Renal Aging: Causes and Consequences. *J Am Soc Nephrol.* 2017;28(2):407-420. doi:10.1681/ASN.2015121308)

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5. Effect of aging on cardiovascular system

I. Heart

Function of the heart shows gradual changes with age , these changes result in minor effects under normal condition and at rest . On the other hand they result in significant effects in abnormal conditions at rest or during exercise such as developing age related diseases.

The pacemaker system undergoes alteration due to develop fibrous and fatty tissues . These alterations represented by replacement of cells of the left bundle branch and loss number of Sino-arterial node cells (SA). Therefore old people may have slower heart rate and cardiac arrhythmia .

Heart increases is size, specially the left ventricle because of an increase in the stiffness of cardiac muscles resulting from increased accumulation of fat and collagen fibers in the cardiac tissue . These changes make the heart less compliance and bigger in size. An increase in the volume of left ventricle leads to an increase in pressure on left atrial and pulmonary capillary, which many result in pulmonary edema and make elderly feel exhausted during exercise. The heart valves may develop abnormalities such as stenosis due to decreased flexibility, moreover heart murmur may be common. Elector cardiogram (ECG) of elderly differs little from ECG of young healthy people . Because of all these age related change in the heart, coronary artery disease and congestive heart disease may develop in elderly.

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II. Blood Vessels

The aorta loses some of its flexibility and becomes stiffer and thicker because of the changes in the connective tissue of walls of the blood vessels. This results in an increase in blood pressure and the load in the heart work ,which in turn lead to hypertrophy of the heart. Other arteries also become stiffer and thicker. The walls of capillaries get thick , therefore nutrients and waste products exchange become slow and less effective. Blood vessels changes with age are illustrated in figure 5.

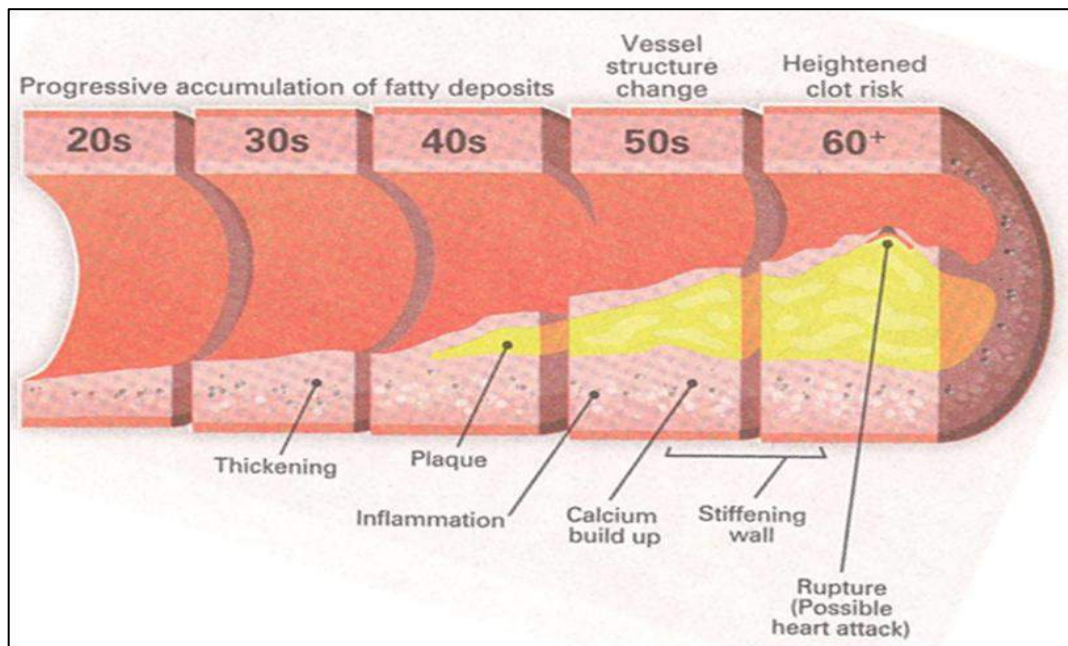


Figure 5: Blood vessels changes due to aging

(<https://foreverlivingdream.com/2012/02/10/what-is-your-arterial-age/>)

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III. Baroreceptors

The receptors that monitor blood pressure become less sensitive to detect the pressure, therefore old people may suffer from orthostatic hypotension (a decrease in blood pressure when person changes the position e.g. from sitting to standing).

IV. Blood Cells and Immunity

In general, blood volume decreases due to the reduced fluid in the blood stream. Production of red blood cells (RBC) is slow, especially in case of anemia, and hemorrhage. On the other hand the number of white blood cells remain unchanged but neutrophils decrease as well as their functional activity declines.

Aging shows reduced ability in B cells response to antigen, therefore generation of antibodies (Ab) and Ab mediated immunity decrease. As a result the ability of old people to resist the infection declines. In addition, the ability of thymus to produce matured T cell decreases as well as the ability of helper T – cell to proliferate. An exposure to antigens produces a reduced number of helper T – cell which reduce stimulation of effectors T – cells, therefore cell mediated immunity decreases.

The activity of cell mediated immunity to resist and fight the pathogens declines. Therefore old people become more susceptible to infections such as influenza and other infections. Moreover, decreased immunity may reactivate the pathogenicity of some remaining pathogens in the body as in certain cases of viral diseases.

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6. Effete of aging on the skeletal system

I. Bone

The changes in the bone are of the most important effects of age on the body. Both quality and quantity of the bone matrix are influenced by age, therefore bone matrix becomes less strength and less flexible than bone matrix of the young adult. Furthermore matrix break down by osteoclast occurs at a rate faster than matrix formation by osteoblasts (figure 6).

The most significant change in bone is loss of calcium , which is due to the disturbance in the Ca^{2+} level regulation by hormones. Cancellous bone is missed because trabeculae become weak and thin. Compact bone begins to lose about age 40 years, (figure 7) The rate of loss increases with age. Other factors that may contribute to bone loss is slow protein synthesis , which affects the collagens fibers what give the bone its strength and flexibility. In general the bone of man is stronger than that of women, due to the effect of testosterone hormone which makes the bone denser.

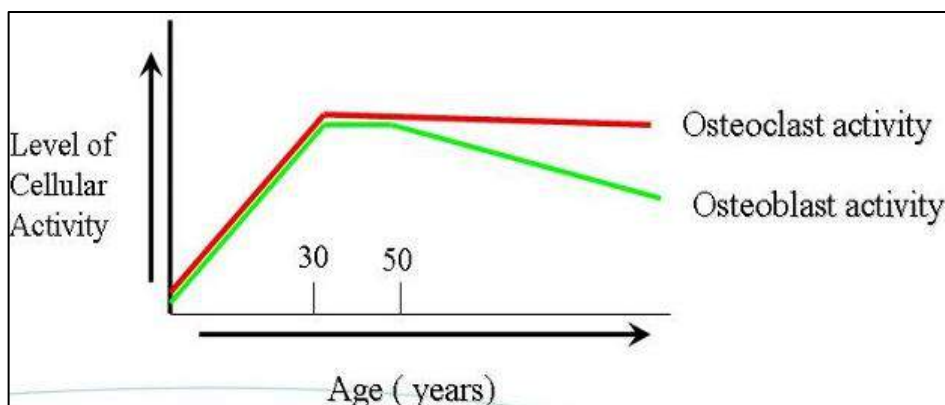


Figure 6: The changes in the osteoclast and osteoblast activity due to aging <http://www.positivehealth.com/article/arthritis/therapeutic-use-of-green-lipped-mussel-extract-glme-in-the-inhibition-of-arthritic-degenerative-joi>

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Moreover bone loss in women is more severe than in men. In women loss of calcium from bone begins around age 30 and increase with age reaching to 30% of calcium lost form bone . On the other hand, in men , calcium loss begins where they reach age 60 .

Loss of bone increases the risk of fracture in old people. These change cause pain , stiffness and deformity. The height may decreases and the spine becomes more curvature. Bone loss makes old people prone to teeth loss . it has been thought at that all these changes occur because of the changes in the hormonal balance and the level of activities.

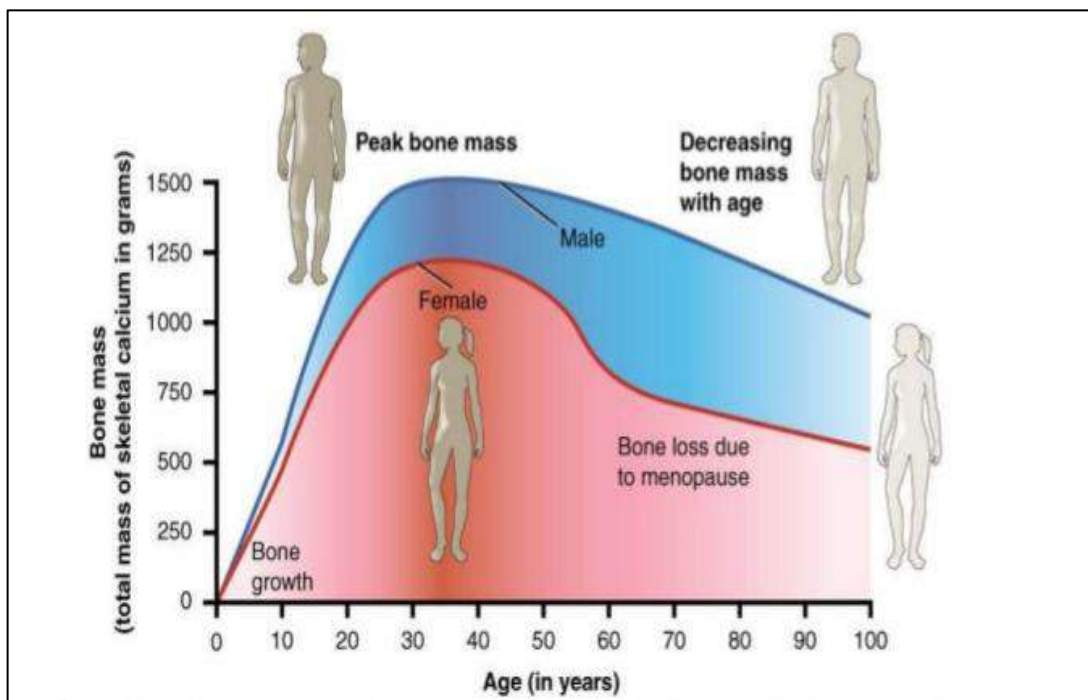


Figure 7:Effect of aging on the bone.

(Exercise, Nutrition, Hormones, and Bone Tissue". Anatomy & Physiology. Openstax CNX. 2013. ISBN 978-1-938168-13-0. Archived from the original on 10 January 2017)

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II. Cartilage and Joints

As person ages the cartilage becomes thinner and wear out. This affects the movements and makes them painful and less flexible. Costal cartilage becomes calcified that resulting in restricted breathing. Fibro cartilage the cartilages that provide cushioning for vertebrae experience loss of water and cells after the age 40 , which lead to decline in the level of cushioning.

The influenced cartilages cause many changes in the joints and synovial joints in a way that may create difficulties and problems to the old people. In addition to the decline in the synovial fluid , elastic and collagen fibers which are responsible for elasticity and flexibility of the tissue. The range of the motility decreases due to shortening and reduced flexibility of the ligaments and tendons. Moreover , the decreased activities of old people lead to further reduction in flexible joints and limit of motions.

III. Muscles

Skeletal muscles mass declines with age. It has been reported that decline in muscles mass throughout the life is 0.37% per year in female and o. 47% per year in male. This percentage in the muscles loss increased when people reach 75years of age in both sex . It has also been found that atrophy in skeletal muscles is accelerated when the physical activities are absent , and the muscle loss is used to be accompanied by a decrease in strength , in a way which may increase the risk of physical impairment and disorders later on. Many factors result in a decrease in muscle strength with age as clarified in figure 8.

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At the myocellular level ,the studies showed a significant reduction in the size of muscle fibers. This reduction depends on the type of the muscle fibers .Type II become smaller in size in about 10 – 40% compared to that in young ,while type I are not affected by age. As well as the total number of muscle fibers reduces. This observation suggested that muscle atrophy with age could be contributed to muscle fibers loss.

The main reason for loss of skeletal muscle is attributed to imbalance between protein synthesis and protein breakdown of the muscle.

Age related contractile function

The contractile function and the excitation – contraction coupling undergo changes. These changes are represented by reduction in the force per unit of area in the skeletal muscle level. The change in the force generating capacity is attributed to the change in the excitation – contraction coupling process (E-CC) of the muscle. E-CC participates in the physiological events that turn the neural signal into muscle contraction and then into force initiation.

The change in elastic fiber is another factor that contributes to the change in E-CC properties . Previous studies * have shown that physical properties of the muscle fiber are affected by intermuscular adipose tissue which in turn may limit motility in old age people. Ectopic fat can induce secretion of inflammatory factors such as cytokines. An increased level of cytokines may reduce the mass of skeletal muscles and their performance when they interact with hormones such as testosterone, growth hormone and insulin and cause resistance to anabolic stimuli. Beside the accumulation of adipose tissue in muscle fiber, muscular fibrosis occurs by formation of fibrous tissue in between muscle fibers .

*Michel tideland , Inez Trouwborst & Brian C. Clark . Skeletal muscles performance and aging. Journal of Cachexia, Sarcopenia and Muscle 2017 . Dol: 10 . /002 / jesm . 12238

3.Chapter Three:Effect of Aging on the Physiology of Body Systems

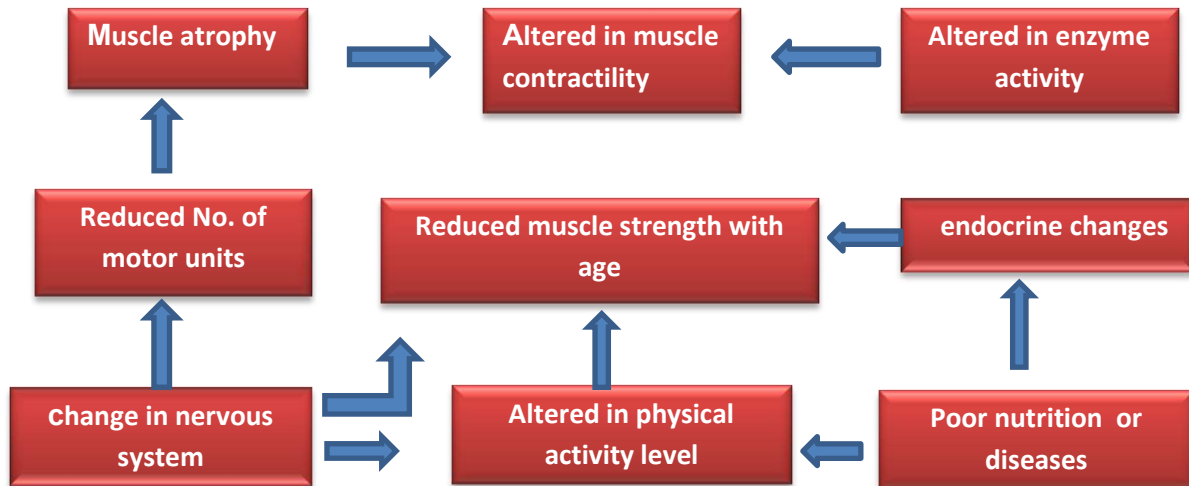


Figure 8 : Factors that lead to the decrease of muscle strength with age.

Porter, M. M., Vandervoort, A. A., & Lexell, J. (1995). Aging of human muscle: structure, function and adaptability. *Scandinavian journal of medicine & science in sports*, 5(3), 129-142.

In fact the degeneration of the anatomical and physiological processes governing these systems results in impairment in muscle performance. These systems are all influenced by life style , biological and psychological factors the physical activities and nutritional habits are essential life style agents. While the biological factors include: genetic, hormones, inflammatory processes and the psychological factors including: stress , fear , loneliness and self – efficacy are of direct or indirect effect on skeletal muscle functions.

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7. Effect of aging on gastrointestinal tract

In general , digestive tract undergoes several gradual changes with age (figure 9). These changes include a decrease in blood supply, secretion of goblet cells of mucosa as well as a decrease in secretion and production of gastric glands.

Smooth muscles cells are reduced in number, therefore the motility of digestive tract declines. This decreased motility makes gastroesophageal reflux disorder (GERD) develops and increases with age. GERD is one of the most important reasons that make old people used to take antacids proton pump inhibitors and the antagonists.

The submucosa and serosa layers become thin. This change besides the reduced secretion of mucus makes the digestion tract less protected against toxic materials.

The phagocyte activity of the hepatic cells declines as well as the liver ability to detoxify the toxic material ,therefore old people are more susceptible to infections and more affected by toxic material which may elevate the risk of ulceration, particularly in old people who used to take non-steroidal antiinflammatory drugs(NSAIDs).Furthermore the increased susceptibility to infection may lead to an increase in bacterial growth which results in decreased absorption of some nutrients such as irons ,vitamin B12 and calcium.

Certain problems and impairments are common in old age such as constipation pathophysiology of swallowing , esophageal reflux and cellular mechanism of neoplasia in the gastrointestinal tract .

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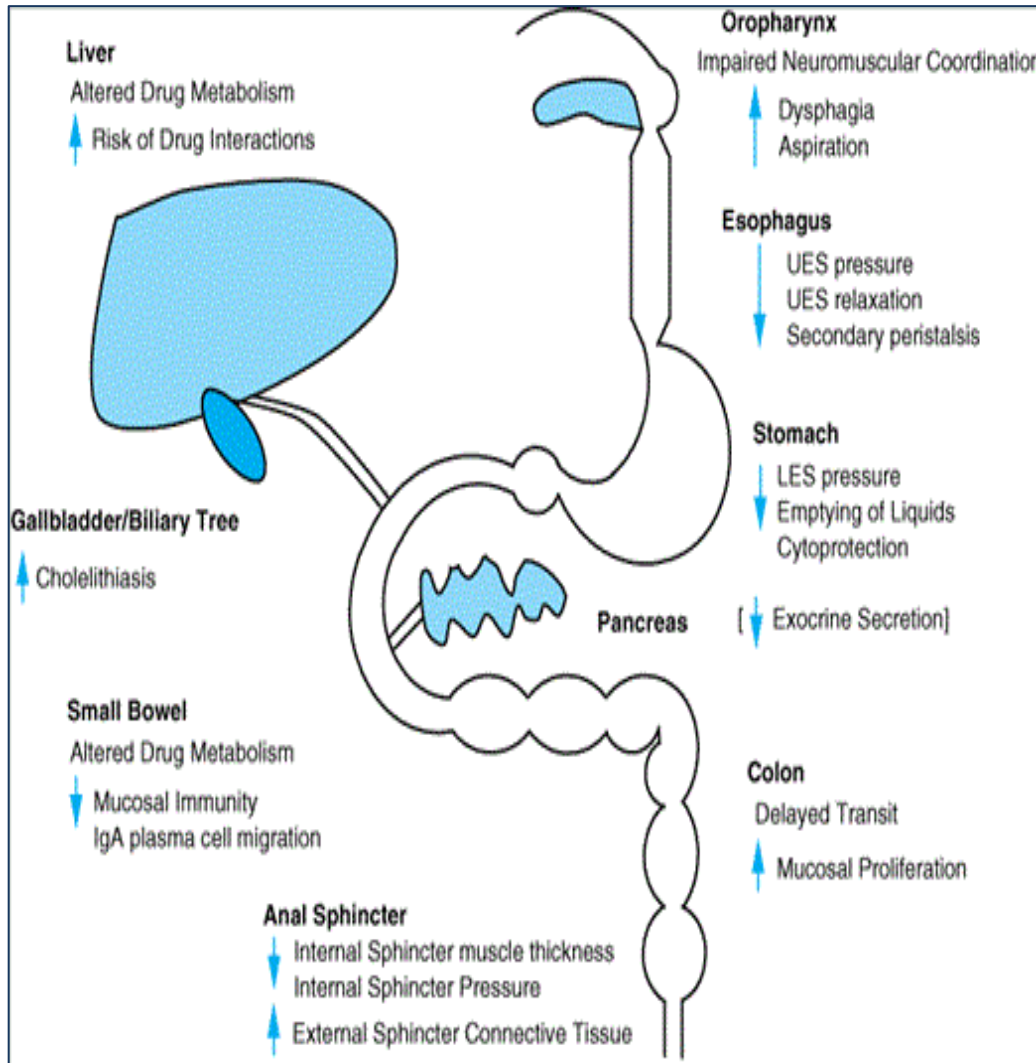


Figure 9 :Effect of aging on gastrointestinal tract.

(HalterJB,OuslanderJG,Tinetti ME,Studenski S,High KP,Asthana S:Hazzard,s Geriatric Medicine and Gerontology,6th ed.New York:McGraw-Hill;2003,http://www.accessmedicine.com).

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8. Effect of aging on endocrine system

The age related endocrine changes are varying in different glands. Some endocrine glands undergo decline in the activity to secrete their hormones. In general endocrine functions show decrease with age due to decrease in the sensitivity of hormone receptors, therefore metabolism and production of the hormone are affected.

Growth hormone(GH)shows changes through the individual's life.GH concentration level increases during childhood and adolescence reaching to the maturation period to accelerate the growing and maturation, while its level decrease after that and continues to decline with age. Decreasing in GH level may lead to many significant effects such as a decrease in protein synthesis, immune function as well as a reduction in bone mass and lean body mass.

Hypothalamus-pituitary-thyroid axis shows different complicated physiological changes. It is important to distinguish and differentiate the changes that result from the effect of aging on this axis and the changes that result from any other pathological condition or age related disease which may alter the physiology of hypothalmo-pituitar axis. However thyroid hormone secretion decreases slightly with age particularly T3 hormone. On the other hand secretion of parathyroid hormones does not change.

Hypothalmo– pituitary – adrenal axis shows inconsistent changes in the effect of adrenocorticotrophic hormone (ACTH) on the secretion of cortisol, as well as inconsistent changes in the effect of cortical on the ACTH. The changes in the circadian rhythm of cortisol secretion may play a role in the etiology of sleep disorders in old age people. The changed level of cortical with age may contribute to the changes in the body composition such as changes in distribution and accumulation of fat.

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Secretion of rennin enzyme by the kidneys decreases which may lead to a reduced response to the decreased blood pressure by the effect of renin-angiotensin mechanism. Aldosterone hormone which regulate water and salt retention declines resulting in dehydration in elderly . Another hormone which is affected by aging is the insulin. Insulin secretion decreases resulting in an increase in blood glucose level particularly after a heavy meal. In some cases, the change in insulin production and activity elevate the incidence of diabetic mellitus , type II.

In fact the clinical consequences of the different hormonal changes are wide, such as insulin resistance, risk of cardiovascular diseases, decline in protein synthesis and immune functions, decrease in lean body mass and bone mass, an increase in fat accumulation, sleep disorder, fatigue and anemia.

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9. Effect of age on the reproductive system

Secretion of reproductive hormones decreases gradually with age, Menopause is the most significant sign of changes in women. Ovaries decline in their activities to produce the follicles and the hormones estrogen and progesterone. On the other hand luteinizing hormone (LH); follicle stimulating hormone (FSH) and sex hormone binding globulin increase. Menstrual cycle becomes irregular and then stops occurring.

Frequency of ovulation decreases by age 40 and the reproductive ovarian function ceases within the next 15 years. Small concentrations of estrogen are continued to be released from adrenal cortex and small amount of this estrogen is converted to estradiol. This changing leads to significant changes such as loss of skeletal mass and increase the risk of cardiovascular problems. Hot flushes are among the most common signs at this period due to changes in the thermoregulatory center in the hypothalamus.

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The size of uterus decrease and the endometrium become less thick; the vaginal wall loses some of its elasticity and lubrication and become more susceptible to different types of infections. Incidence of ovarian cancer; uterine cervix cancer; endometrium cancer; as well as breast cancer increase with age.

Hormonal replacement therapy is recommended sometimes particularly in severe cases of menopausal sign but for short time, otherwise it makes the patients at risk of many healthy problems such as ischemic stroke, thrombosis and breast cancer. Despite that hormonal replacement therapy may be workable and of great benefits in some cases, there is no magic tablet that may opposite the effect of aging processes and that GH therapy as anti-aging has not been proved to be of a potent effect in older individual . More studies are required to prove the effectiveness and safety in old people.

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In man, there is a gradual decrease in serum testosterone level but there is no specific point at which the testosterone begins to decrease in old man and without any clear out come. The decrease in the serum testosterone level results from the change at the level of hypothalamus – pituitary axis. LH and FSH increase in old man and the response of testosterone to the increase in LH and human chorionic gonadotropic (hCG) decrease, as well as the circadian rhythm of testosterone level through the day is lost.

The clinical feature resulting from decreased testosterone level include: decreased body components of bone and muscles, poor libido, erectile deficiency, fatigue, insulin resistance and may extend to develop cardiovascular problems.

Longitudinal studies have suggested that testosterone supplement in old men who suffer from with decreased testosterone level may moderate or even prevent the signs of aging.

Chapter Four

How to improve aging

4.Chapter Four:How to improve aging

Aging is a continuous, progressing process and lifelong, therefore, the changes cannot be stopped. Different instructions and tips may help to get along with aging positively. Despite the changes with age cannot be prevented, several factors besides a healthy lifestyle may reduce the risk of age related diseases and decrease some serious conditions that occur with age, therefore old people should follow several strategies to maintain and improve life quality with age. There are several factors that may play an important positive role in aging and life expectancy such as healthy life style, physical activities and etc.

I. healthy lifestyle

A healthy lifestyle is the life style that keeps an individual healthy and wellbeing. To be healthy, this means that individual is in fit states: physically, emotionally and mentally. Hence keeping healthy lifestyle may enable old people to resist different diseases such as infectious diseases and may even prevent some age related diseases and chronic diseases that may develop due to neglecting what is right and necessary to a healthy boy.

Some of the most influential factors of healthy life style include eating healthy food and maintaining healthy weight. Eating healthy food and balanced diet rich in grain, vegetables, fruits and substitute unsaturated fat for saturated may protect the body against some age related diseases, heart diseases, atherosclerosis and diabetes.

Fruits and vegetables especially green leafy vegetables are rich in antioxidants which neutralize the free radicals effects. Some kinds of fruits such as prunes, blueberries, black berries and kale contain high amounts of antioxidant. Studies suggest that mediterranean style diet which based on whole grains, fatty fish such as salmon and tuna and mono-unsaturated fat such as nut and olive and are of great benefit for

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health. Other type of food may be considered as anti-inflammatory food such as turmeric and dark chocolate. Studies have found that daily intake of calcium and multivitamins could help in the improvement of health status of in old people. About 1200 mg calcium per day for both men and women over 50 years is recommended .While 600 international unit(IU) per day of multivitamins for people under 60 years and 1000 IU per day for those over 60 years is the appropriate dose . On the other hand limit intake of sugar filled food may help , because excess amount of sugar can combine with portions in the body resulting in Advanced Glycation End Products (AGES).

AGES are thought to play a role in speed up aging process by alerting free radicals activity and promoting the inflammatory processes . As well as AGES play a role in the pathogenesis of diabetes by making the blood more viscous and sticky which affect blood ability to flow softly through the capillaries and into extremities and vital organs like eye and kidney. American heart association recommended that women should not consume more than 100 calories per day of added sugar and men should not consume more than150 calories per day. One of the most important influential factor is to avoid smoking and alcohol.

Effect of smoking and alcohol

It is well known that smoking is one of most important health issues that affects the key elements of healthy and youthful appearance. These elements such as collagen and elastin as well as other tissues are destroyed by the damaging and inflammatory effect of smoking. Thereby, smoking habit is highly related to many health problems and diseases that may threaten people's life such as cardiovascular diseases , COPD and lung cancer. Besides, its damaging effect on the internal tissues, smoking can highly affects the skin , teeth and eyes . It makes aging process run at faster rate comparing with aging process of nonsmoking people.

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Effect of smoking on the eye.

Because of the damaging, inflammatory effect of smoking as well as reduced blood, bags under the eye may appear, giving the eye its tired and unhealthy appearance. In spite of the presence of many ways to minimize the negative effect of smoking the only workable way that reduces the harmful smoking effect on aging here is to stop smoking.

Effect of smoking on the skin

Skin undergoes many changes due to the effect of aging process, such as appearance of wrinkles. These changes appear faster among smoking people than those who never smoke. This effect is caused by factors such as damaging effect on collagen, elastin and other tissues. Furthermore, smoking may impede the vitamins and the oxygen from reaching the skin. All these reasons give the smoking people much older appearance.

Effect of smoking on teeth

Oral health has many important repercussions including gum diseases, unnecessary pain, poor nutrition as well as different other serious diseases related to gastrointestinal diseases, diabetes and heart diseases. In general, cigarette smoking has a harmful effect on oral health and especially on teeth. It contributes to gum diseases and makes the dentist less effective, providing factors that lead to early dental failure in smoking old people.

Effect of smoking on the voice

Smoking affects the voice in different ways. Vocal cords are damaged and dried by the continuous exposure to smoke. Inhalation of carbon dioxide and other chemical materials may reduce blood flow and oxygen demand to different body parts.

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Moreover long lasting smoking is the major cause of upper and lower respiratory airway diseases such as chronic bronchitis, allergic bronchitis and other types of COPD.

II. physical activities

Inert life style may create serious health problems .Physical activities and regular exercises have many positive significant effects for both body health and mind. Regular daily exercise and even light exercise such as gardening and housekeeping may keep some body systems such as cardiovascular system and skeletal system healthy. Moreover, it has been found that physical activities just like mental activities in keeping mental capabilities and reducing the risk to develop dementia.

Body shape is an important criterion of fitness .Studies has found that people of both sexes who have more accumulated fat around the abdominal area have higher tendency to develop cardiovascular diseases than people who have more accumulated fat around the hips. Hence, regular exercise and different physical activities have great role in living healthy. Furthermore it has been proved that regular exercises may limit the decline in the functional activity of endocrine system .For example, growth hormone (GH) secretion declines with age ,but this decline is not the same rhythm for all old people .It is less significant decline with age in people who used to do regular exercises.

III. General health care

General routine testing to monitor health status such as blood pressure, blood glucose, cholesterol, lipid profile and osteoporosis may work to prevent development of serious diseases and disorders as well as treating disorders which can be cured such as infections. It is recommended to have a vacation from time to time at any age to reduce the role of stressful conditions that negatively affect immune system. All these factors may work to increase life expectancy.

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IV. Living in healthy environment

The continuous exposure to the environmental toxins or polluted environment by different harmful gases and create serious health problems such as chronic respiratory diseases different nervous system disorders and different kinds of cancers that can shorten life expectancy even to those people with good genetic matchup.

V. Social activities

Social activities play an effective role in the life of old people, because they are highly related to cognitive functions. Cognitive function is among the factors that suffer from impairment with age. Cognitive function is a set of mental abilities including processes like thinking feeling, attention, hearing and memory that need to knowledge.

Researches have proved that social activities are of positive significant effect on cognitive functions of elderly, because they provide a resistance to many psychological and mental diseases. Furthermore social activities have the ability to reduce the decline in the cognitive function.

Old people with cognitive decline suffer from risk of functional dependence and inability to meet their personal requirements .They are likely to perform some daily activities but with extra continuous care and attention from their families. According to the world Alzheimer report, the number of dementia worldwide is significantly increased to reach 131. 5 million by 2050.Cognitive decline is interpreted by Alzheimer diseases and other dementias. It begins to occur after midlife and mostly at old age .

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It has been found that cognitive decline is related to many factors such as chronic diseases, life style , social activities and artworks . Hence participating in different social activities that may reduce the negative effects of aging in population was recommended among elderly people.

Different studies around the world have revealed the positive role of social activities in cognitive function. A study* in Japan found that participation in social activities was related to independent daily works. Another study ** in Korea has concluded that absence of social activities may increase the risk of depression ,as well as researchers from us*** showed that deficiency in the social activities result in an increase in cognitive functions decline. Also there are few studies in the developed countries have concentrated on the role of social activities in cognitive function of old people. A study in China**** showed the differences in the effect of social activities in men and women and that women get more benefits than men do. Moreover, some evidences suggest that challenging activities such as learning a new language and playing new games as well as continuous reading can provoke and keep the mind sharp and active.

*Tomioka ,K.; Kurumatani ,N.; Hosoi ,H. Association between social participation and Instrumental Activities of daily living among community Dwelling Older Adults.J.Epidemiol.2016,65,107-113.

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VI. Hereditary factor

Although the pervious mentioned factors are highly influential in aging, hereditary factor still the decisive factor that determines a person ability to develop some disorders and affect life expectancy. It is confirmed that living to a very old age is an issue that inherited in families. People who have protective genes against specific diseases such as coronary artery diseases and some kinds of cancers are more likely to have longer life. While people who inherit genes responsible for developing high level of cholesterol are more likely to have shorter life.

The Alliance for Aging Researchers has recommended *ten* items in order to keep the youth of the brain.

- Playing challenging games that prowled the mind.
- Taking a class or course to learn new subject.
- Exploring new hobbies and new personal possibilities.
- Writing an autobiography or making history scrapbook of the family.
- Visiting a new place.
- Organizing actives for family numbers or friends.
- Writing letters to the loved person.
- Working as volunteer with nonprofit organizations.
- Starting a new part time job.
- Keeping a dream journal.

Glossary

LTL	Leukocyte Telomere Length
CR	Caloric Restriction
IGF1	Insulin like Growth Factor 1
ROS	Reactive Oxygen Species
MIP	Maximum Inspiratory Pressure
TDP	Transdiaphragmatic Pressure
MVV	Maximum Voluntary Ventilation
RV	Residual Volume
VC	Vital Capacity
FEV1	Forced Expiratory Volume at the first second of expiration
TV	Tidal Volume
MRV	Minute Respiratory Volume
ERV	Expiratory Reserve Volume
AV/Q	Ventilation Perfusion ratio
COPD	Chronic Obstructive Pulmonary Diseases
ADH	Antidiuretic Hormone
ECG	Electrocardiogram
GERD	Gastroesophageal Reflux Disorders
GH	Growth Hormone
ACTH	Adrenocorticotrophic Hormone
hCG	human chorionic gonad tropic

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