Age-Related Diseases

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Abstract

Age-related diseases occur frequently in the older population which signifies age as a major risk factor for old age disorders. Aging itself is not a disease but there are certain manifestations associated with aging that contribute to age-related diseases. There are many underlying causes that exacerbate age-related disorders, they include, inflammation, exposure to environmental pollutants, radiation, lifestyle, and dietary conditions. These factors tend to affect different people at a different rate and the disease progression depends on cellular aging and molecular pathways. Some of the prominent diseases associated with aging are cardiovascular, neurodegenerative, and metabolic in nature. Currently, many research models are proposed to determine the effect of aging on human body and how the rate of aging can be reduced by changes in lifestyle, specially controlling the social and mental stressors that catalyse aging by causing early cognitive impairment.

Keywords

Aging theory · Neurodegenerative diseases · Cognitive function

3.1 Normal Aging and Its Manifestations

Aging is an inevitable process. During this time, all organs tend to lose work as they age. Therefore, aging is basically a decline in the regenerative and reparative potential of tissues and organs. Aging takes place on various levels and there are

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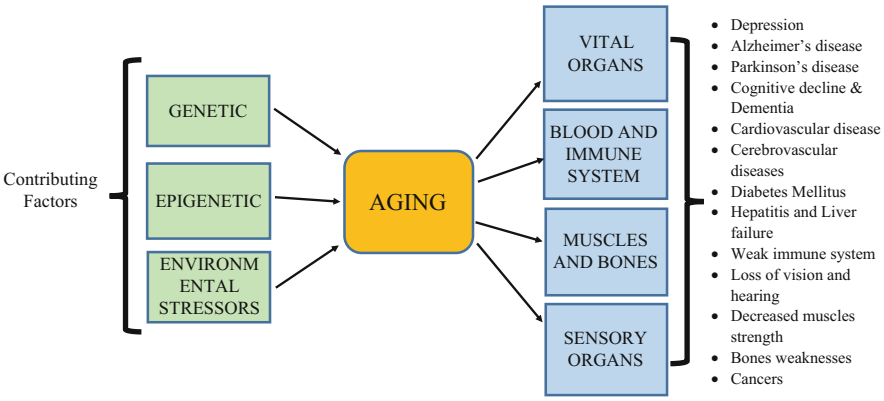

Fig. 3.1 Main contributors of aging associated diseases

factors like epigenetics and hereditary changes responsible for it (Roberts and Allen 2016). Along with this, many cells lose their function because there is an increase in the levels of pigments and fatty substances in the cells. As aging continues the waste materials build up inside the cells, airways and the organs become less efficient. This altogether leads to an altered cell membrane permeability (Gemma et al. 2007).

Aging is a slow and gradual process and continues throughout our lives. All our organs lose function with time. For example, the pumping ability of the heart of a 20 year old is about 10 times more efficient than that of a person aged 30–40 years. Organs like heart, kidneys, and lungs undergo substantial amount of changes, and such changes occur slowly over time (Gladyshev 2016). Whenever an organ undergoes a lot of stress or work, it results in abnormalities like sudden heart failure. Certain factors like medications, sudden increase in physical activity or change in environment tends to increase the work load on the organs. Aging also makes it difficult for the body to remove the drugs from the body as the kidneys and liver function at a slower rate (López-Otín et al. 2013) (Fig. 3.1).

3.1.1 The Aging Theory

Aging remains an enigma for the biologists (Gladyshev 2016). Various theories have been put forth to solve the mysteries associated with aging and its mechanisms. According to some theories, aging results due to the ultraviolet light exposure over time that causes injuries. Other studies have established that aging is controlled on the genetic level. There is no single process that can explain aging, as it is a complex phenomenon which varies and affects different people in entirely different patterns and diverse rates (Gemma et al. 2007).

3.1.2 Aging Cells and Their Replacement Mechanism

As cells age, they become less efficient in doing their normal duties. There has to be a mechanism where the old cells must die, as a normal feature of the cells. This process is called apoptosis where a sequence of reaction is initiated by the genes, that results in cell death. This is important because only in this way, the old cells will create room for the new ones (Saretzki and von Zglinicki 2002).

3.1.3 Telomeres and Aging

Telomeres are structures made from protein and DNA, present at the end of chromosomes which serve to protect the overall genome from degradation. Therefore, telomeres tend to preserve the genetic information. As part of normal cell division, a very small region of telomere is lost. Upon reaching a certain telomeric length, the cell senescence occurs and enters into the apoptotic phase. The telomere length therefore, determines the lifespan of a certain cell or organism. However, there are many external factors, i.e. lifestyle changes that may fasten this process and brings about early aging and health deterioration. The factors responsible for early aging and shortening of telomeres include obesity, exposure to pollution, unhealthy diet, and stress, etc. (Shammas 2011).

The evidence for the telomere aging hypothesis comes from the finding that the telomeres in the normal human cells (young individuals) shorten when they are grown in cell culture (Shay and Wright 2001). Some telomeric proteins like TRF1, TRF2, TIN2, TPP1, Rap1 are expressed almost all the time. Other proteins are expressed transiently, for example, the telomerase enzyme. Telomerase is a reverse transcriptase enzyme and it works by extending the 3′ end by adding TTAGGG repeats at chromosome ends. Therefore, it is important for a cell to have normal telomerase activity so that the integrity of chromosomes is maintained. In case of accelerated telomere shortening, manifestation of a number of age-associated diseases like diabetes, heart failure, osteoporosis, increased cancer risk takes place (Aubert and Lansdorp 2008).

According to studies, due to shorter telomere length, older people have three to eight times higher affinity to encounter infectious diseases or heart related disorders. In order to delay the signs of aging due to telomere shortening and to help protect telomeres, a number of antioxidants can be added to regular diet. These antioxidants are found in foods like salmon, tuna, sesame seeds, chia seeds, green tea, black raspberries, olive fruit, kiwi, red grapes, etc. (Shammas 2011).

3.1.4 The Role of Mitochondria in Aging

Mitochondria plays a significant role in the manifestation of age-related disorders, most importantly, the neurodegenerative diseases. Apart from energy production, mitochondria is involved in a number of functions, like calcium homeostasis,

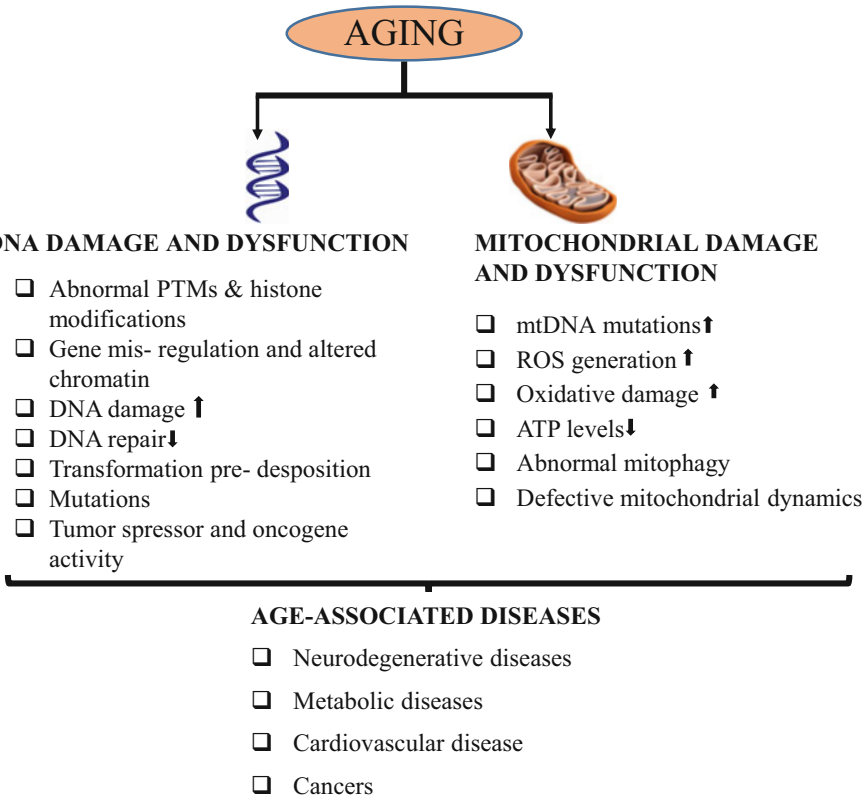

Fig. 3.2 Aging leads toward different diseases by cell structures damage

oxidative phosphorylation, and cell signaling to the nucleus in states of stress. It also participates in apoptosis and formation of cell's free radicals. The fact that mitochondria plays an important role in overall aging process is because it has a reduced DNA repair capacity and has an estimated tenfold greater rate of mutation than nuclear DNA (Haas 2019).

According to a study by Peter McGuire, the major player in aging of a cell are the mitochondrial damage-associated molecular patterns (mtDAMPs), which when released activates a number of proinflammatory cytokines like TNF-a, IL-1, IL-6 (McGuire 2019). This in turn results in an enhanced inflammation, declining function of T cells and susceptibility to viral infections in the older individuals (Jang et al. 2018) (Fig. 3.2).

3.1.5 Aging Organs

The optimal working of the organ depends on how well the resident cells function. The cells that are old have altered function compared to the new cells. Also in some

organs, the number of total cells decrease as aging proceeds, for example, in the testes, kidneys, and liver. There are certain conditions in the elderly where the progressive loss of nerve cells leads to neurodegenerative disorders like the Parkinson's disease or the Alzheimer's disease (Wang and Bennett 2012). The loss of function of one organ may affect the efficiency of other organ and contribute altogether towards aging. For example, atherosclerosis results when the blood vessels are narrowed due to the accumulation of cholesterol, as a result the organ will not function well because the blood flow has been decreased (Gemma et al. 2007).

In the aged individuals, majority of the functions stay normal but the reduction in overall function of organs is due to the fact that they are less able to handle different stresses. These include extreme temperatures, strenuous physical activity, disorders, effects of drugs, etc. (López-Otín et al. 2013).

3.1.6 Signs of Aging

As aging proceeds, different people show different sings. But some of the common are as follows:

3.1.6.1 Sensory Changes Associated with Aging

As age advances, the risk of certain chronic hearing and vision related disabilities also increases which results in a decline in overall health and well-being. In the UK, about 27% (one in four) of aged adults 61–80 years suffer hearing disability (Crimmins 2018). Among adults aged 65 years, 13% have a vision impairment. Therefore, hearing and vision impairment is very common in aged population around the world (Cavazzana et al. 2018). One interesting finding suggests a link of hearing and vision impairment with disability, frailty, cardiovascular disease (CVD). However, these impairments are said to be preventable to some extent. The conditions like CVD, frailty, and disability can therefore be avoided if the hearing and vision impairments are addressed in time (Liljas 2017).

3.1.6.2 Hearing Loss

Hearing loss advances with age and is said to affect over half (55%) of the adults aged 75 years or more. Such losses can be prevented by the use of hearing aids. Hearing loss, other than aging, also occurs due to continuous exposure to loud noise. The loss which is age associated is called presbycusis (Huang and Tang 2010). During this phase it is also very difficult for the people to make sense out of the words because they cannot identify the consonants that are high pitched (k, t, s, p, and ch).

3.1.6.3 Vision Related Deficits

A change in a person's vision is usually the first sign of aging. As people age, the following vision related deficits takes place:

- The focal point of the eye becomes hard, which makes focusing on near objects harder.
- It becomes harder to see in the dim light as the focal point becomes denser.
- The eyes generally encounter dryness as the number of cells required for lubrication of the eye, decrease in number. Tear production is also reduced.
- The number of nerve cells also reduce in number, disabling the accuracy of perception.
- The focal point of the eye becomes yellow, it changes the way a color is perceived in normal conditions (Fine et al. 2000).

Loss of Close Vision The elderly population, in their late 1940s usually complain about a discomfort whenever they observe an object closer than 2 feet. This condition is called presbyopia, where the focal point of the eye hardens. Usually, in order to assist the eye to the center, the lens changes its shape. Because a stiffer focal point makes focusing on the near objects very difficult. At the later stages in life, almost everyone goes through presbyopia and needs amplifying glasses (Khan et al. 2017).

Color Perception Changes As the focal point tends to become yellow with time, colors are observed quite differently. It also becomes harder to differentiate between different colors. Specially the blue color may seem more gray and the blue background is indistinguishable (López-Otín et al. 2013).

Age Aged Individuals Need for Brighter Light to View Things Consequently, the pupil of eye reacts very slowly in response to light. A very slow reacting pupil in the elderly makes them unable to see when they first enter a very dark room or become blinded for few moments when they enter a very bright room. The pupil widens and also narrows bringing less amount of light inside. This increased sensitivity to the amount of light is because of cataracts or areas that have darkened in the lens. Older people often see many dark spots moving in their field of vision. These are called "floaters," which are small regions of normal fluids that have become solid over time. They do not usually interfere with the vision but can cause blurry images. Not only is the function of eye affected, its physical appearance also changes considerably (Stuen and Faye 2003).

- The sclera of the eye (white region) gradually turns brown or yellow. This happens due to continuous exposure to wind, dust, and UV light.
- People with a darker complexion may experience random blotches in the white region of the eye.
- Calcium and cholesterol accumulation may appear as a grayish white ring on eye surface called arcus senilis. However, vision is not affected by this.

- As the muscles around the eyes droop, and tendons stretch the lower eyelid tend to hang away. This results in a condition called ectropion, which tends to interfere with lubricating the eyeball thus making eyes dry (Liljas 2017).

3.1.6.4 Disturbances in Vestibular Functions During Aging

About 30–35% of older population suffers from the vestibular dysfunction. One common type of vestibular disorder in the elderly is benign paroxysmal positional vertigo (BPPV). Not only this but the elderly aged 65 face vestibular dysfunction due to injurious falls annually. This results due to balance impairments, and the older people experience more imbalances due to aging of the nervous system (Balatsouras et al. 2018). Such changes also impair walking capabilities, the elderly tend to walk with more care and slower pace to avoid any falls. The dysfunction of the vestibular system also leads to an altered spatial navigation. Aging altogether brings about rapid changes in the somatosensory function of an individual which manifests itself as visual impairments, decreased strength, and cognitive decline. The older adults are more prone to a decline in cognition and vestibular dysfunction mediates this decline (Shaffer and Harrison 2007).

3.1.6.5 Decline in Muscle Strength as a Consequence of Aging

As the aging progresses, usually by the age of 30, the overall muscle strength decreases. Major reduction in muscle strength takes place due to physical inactivity and reduced levels of growth hormones and testosterone. Moreover, muscles are unable to contract more frequently because the fast contracting muscle fibers are lost over a period of time. A case where extreme muscle loss takes place is called sarcopenia, which happens due to inactivity for a longer period of time, aging may or may not play a role in this situation. The regular decline in muscle strength accounts for about 10–15% in an adult's life and even this can be prevented with regular exercise and healthy lifestyle (Jaul and Barron 2017).

3.1.6.6 Immunosenescence (Age-Related Changes in the Immune System)

Immunity play a crucial role in age-related changes, which are mediated by a chronic inflammatory state that leads to aging of the immune cells. The immune cells like the B cell and T cells repertoire undergoes a decline in generation, activation and results in dysfunction. This results in an overall reduction in a body's strength to fight with different infections (Gruver et al. 2007). For instance, the infections of influenza and herpes zoster are common in the elderly and its vaccine is also not very effective. This implies the reason of slow healing of the wounds in older adults because of a delayed immune response. The total number of macrophages, neutrophils is also reduced resulting in an altered phagocytic activity (Jaul and Barron 2017).

3.2 Aging Associated Diseases

What is the reason for experiencing an overall decline in mental and physical health as aging progresses? A unit hypothesis clarifying the pathophysiology of various degenerative abnormalities in various organs, including Alzheimer's, Parkinson's, and other neurodegenerative issues, rheumatoid arthritis, atherosclerosis, and other cardiovascular sicknesses, macular degeneration, and diabetes, has been proposed to clarify how the physiological procedure of aging may prompt different diseases. This idea called the "free radical theory," at first proposed by Harman, gives the most conceivable underlying reason for aging (Harman 1992). The fundamental reason of this hypothesis is that aging and its related manifestations are the net result of free radical-instigated harm and the lack of ability to balance these progressions by anti-oxidative safeguards. The formation of reactive oxygen and nitrogen species (ROS furthermore, RNS) initiates the transcription elements that exacerbates inflammation. The constant expression of such elements over a prolonged period leads to targeting the cells and organs leading to aging related diseases. This oxidative pressure and consequent incessant aggravation is a major factor that leads to majority of the aging related illnesses (Sarkar and Fisher 2006). A summary of the aging associated diseases and their mechanisms is given in Table 3.1.

3.2.1 Contributing Factors for Aging Related Diseases

3.2.1.1 Social and Environmental Conditions

Two important predictors for a prolonged life are wealth and marriage. On the other hand, social seclusion envisages mortality and other hostile consequences in adults. Around 5% of older adults in their 80's are leading an isolated life devoid of basic health necessities, which makes them susceptible to different diseases (Waite 2018). Around 13% of women and 8% of men above 85 years are residing in nursing care or other healthcare locales. These rates are decreased in recent times probably as a result of a lesser amount of disability and enhanced care alternatives at home.

Around 17 million people worked as family caregivers and volunteers to older adults during 2011 in the USA. Caregiving is characteristically an extended obligation and the work hours may well vary in accordance with the requirements of the patient. Individuals suffering with dementia are in dire need of constant care and support. Therefore, the family caregivers must have proper training, counseling, and employment facilitation to help the elderly patients with daily chores (Jaul and Barron 2017).

3.2.1.2 Polypharmacy and Hospitalization

Polypharmacy is described as the simultaneous use of 5 or above prescriptions to a sole patient. Such high number of medications come with a high probability of hostile drug reaction or drug–drug interaction. It may escalate the danger of falls, disabilities, and other harmful consequences (Hajjar et al. 2007). The care providers should be careful while prescribing medicines and should make note of any side

Table 3.1 Different age-associated diseases and their mechanisms

Aging associated diseases	Aging induced disease mechanisms	References
Cardiovascular diseases	• Reduction of nitric oxide release • Reduced turnover of endothelial cells • Disrupted NADPH oxidases mediated ROS signaling pathways • Increased oxidative stress	Yang and Ming (2012), Sahoo et al. (2016), and Izzo et al. (2018)
Cerebrovascular diseases	• Increased oxidative stress • Amyloid beta accumulation • Neuronal damage due to increased ROS level • Reduced neurotransmitters levels • High iron accumulation in brain	Hirai et al. (1996), Patyar et al. (2011), and Izzo et al. (2018)
Hypertension	• Increased NO production due to reduced superoxide dismutase production • Increased expression of matrix metalloproteinases • Activation of transforming growth factor beta-1/SMAD, proinflammatory and profibrotic signaling pathways • Up-regulation of glacetin-3	Jun et al. (1996), Taddei et al. (2006), and Harvey et al. (2016)
Osteoarthritis	• Accumulation of advanced glycation end products (carbohydrate reacts with protein) in aged people lead to reduction in type II collagen of cartilage structure causing bone perforation • Reduced expression of Unc-51-like kinase, Beclin1, and microtubule-associated protein 1 light chain 3 (all involved in regulation of autophagy) leads to cartilage fragility and bone deformation • Reduced level of cartilage glycosaminoglycans leads to knee destabilization • Age-related increase in inflammatory cytokines and chemokines like IL-6 or TNF-α lead to joint tissue destruction and cell senescence	Hamerman (1993), DeGroot et al. (2004), and Greene and Loeser (2015)
Osteoporosis	• Increased ROS production causes reduced production and survival of osteoclasts, osteoblasts, and osteocytes by activating FoxO • Activation of peroxisome proliferator-activate receptor γ by ligands produced from lipid oxidation leads to age-associated reduced bone formation • Increased glucocorticoid production causes bone fragility	Riggs et al. (1998), Manolagas (2000), and Manolagas (2010)

(continued)

Table 3.1 (continued)

Aging associated diseases	Aging induced disease mechanisms	References
Diabetes mellitus	• Age-associated increased hypothalamic transforming growth factor beta induces hyperglycemia and glucose intolerance • Aging induced excessive production of inflammatory cytokines like IL-6 or TNF-α, C-reactive protein, and several cell adhesion molecules lead to increased recruitment of MHC and T cells and pancreatic beta cells leading to their destruction • Accumulation of ROS cause pancreatic cell damage • Accumulation of advanced glycation end products leading to kidney cells damage which ultimately cause diabetes	Davidson (1979), Vlassara (1996), Yin and Chen (2005), Morley (2008), Yan et al. (2014), Guarner and Rubio-Ruiz (2015), and Palmer and Kirkland (2016)
Cancers	• DNA methylation in CpG islands of genes like p16, p53, IB1, ER, IGF2, N33, and MyoD leads to tumor initiation and progression • Decline in the level of sirtuin protein family (involved in certain metabolic processes and also protects against certain stressors) leads to metabolic abnormalities and activation of oncogenes • Decreased levels of circulating B cells and T cells possibly due to age-related diminished follicular dendritic-cell function, leads to immunosenescence triggering tumor initiation • Reduced glutathione level leads to accumulation of ROS which can cause neoplasia	Ahuja and Issa (2000), Hakim et al. (2004), Hall et al. (2013), and Shay (2016)
Liver diseases like non-alcoholic fatty liver disease, hepatitis, etc.	• Decreased levels of serum albumin and bilirubin • Increased level of cholesterol, fats, gamma-glutamyltransferase, and alkaline phosphatase • Abnormal degradation of proteins damaged and denatured by oxidative stress cause accumulation of lipofuscin inside liver cells which cause increased levels of ROS, decreased mitochondrial number and function, and decline in ATP levels in liver cells • Defenestration of endothelial cells lead to deposition of lipoprotein-like chylomicron in liver triggering autoimmune diseases • Reduced number of Kupffer cells in old age leads to accumulation of antigen-antibody complexes and nanoparticles like senescent cell fragments in liver	Sheedfar et al. (2013), Kim et al. (2015), and Aravinthan and Alexander (2016)

Chronic obstructive pulmonary disease	• Neutrophils, macrophages and monocytes show enhanced ROS production in old age leading to increased oxidative stress • Oxidative stress causes shortening of telomeres which cause lungs inflammation by increasing the levels of proinflammatory cytokines • Accumulation of advanced glycation end products cause increase in levels of proinflammatory cytokines • B and T cell levels decrease with advanced age leading to immune deficiency in lungs • Changes in extracellular matrix	Faner et al. (2012) and Barnes (2014, 2016)
Age-related macular degradation	• Elevated accumulation of amyloid beta in retina with advanced age • Accumulation of ROS in retinal pigment epithelium leads to degradation of constantly shed apical photoreceptor outer segment leading to blindness • Accumulation of intracellular lipofuscin and extracellular drusens contained advanced glycation end product, high levels of oxidized low-density lipoproteins, and oxysterols leads to retinal inflammation • Abnormal activity of heat shock proteins and proteasomes due to oxidative stress lead to failure in removal of misfolded proteins causing retinal pigment endothelial degradation • Increased production of inflammatory cytokines cause autophagy in retinal pigment endothelium	Kinnunen et al. (2012), Wang et al. (2012), and Rickman et al. (2013)
Decreased blood cells production	• Hematocrit changes like salt depletion, capillary leakage, sudden release of vasoactive agents, and iatrogenic factors due to aging • Fibrinogen accumulation leading to RBC inflammation • RBC inflammation causes release of inflammatory cytokines and damage to other blood cells • Altered Na+, K+ ATPase activity of blood cell membranes • Altered viscosity of blood due to aging • Impaired autoimmune responses of suppressor T cells to altered self-antigens in old age	Naor et al. (1976), Ergen and Goodell (2010), and Simmonds et al. (2013)

(continued)

Table 3.1 (continued)

Aging associated diseases	Aging induced disease mechanisms	References
Immune disorders	• Increased production and accumulation of ROS in old age leads to excessive inflammatory substances release • Thymic atrophy in old age causes decreased production of B & T cells leading to immune compromised individuals • Reduced telomeres shortening in advanced age leads to DNA damage which ultimately causes elevation of proinflammatory cytokines which as a result affect nearby cells and continue an inflammatory process • During aging process, the process of autophagy cleansing declines leading to mitochondrial disordering and protein accumulation	Prelog (2006), Xia et al. (2016), and Weyand and Goronzy (2016)
Frailty syndrome	• Accumulation of ROS in advanced due to decreased levels of certain antioxidants like glutathione, etc. causes oxidative stress • Oxidative stress causes release of certain inflammatory cytokines like IL-6, TNF-alpha, etc. and their accumulation in cells • Increased inflammation causes more recruitment of immune cells which cause cell destruction, mitochondrial, and DNA damage • Increased serum levels of C-reactive protein, low serum levels of 25-hydroxyvitamin D and growth hormone IGF-1 cause decline in muscle mass and function leading to frailty	Ble et al. (2006), Topinková (2008), and Chen et al. (2014)
Cognitive decline and dementia	• Reduced function of mitochondrial uncoupling protein- 5 (UCP-5) responsible for neuronal metabolism and homeostasis leads to abnormal metabolism in neurons and accumulation of ROS • ROS accumulation causes increased oxidative stress which leads to mitochondrial autophagy • Increased oxidative stress also leads to excessive release of inflammatory cytokines which recruit more immune cells adding to neuronal autophagy • ROS accumulation also causes DNA and protein damage • Damaged and misfolded proteins start accumulating in neurons • Age-related reduction in the functions of insulin like growth factor-1 (IGF-1) & sirtuins, and mRNA abnormal translation further add to accumulation of misfolded proteins	Deary et al. (2009), Bishop et al. (2010), and Terrando et al. (2011)

Alzheimer's disease	• Age-related decline in anti-oxidant such as glutathione levels causes accumulation of ROS in brain leading to oxidative stress • Increased oxidative stress causes DNA damage and proteins misfolding • Amyloid beta and tau proteins start accumulating in the brain causing neurofibrillary tangles • Increased glucocorticoid accumulation in hippocampus leads to increased calcium influx through voltage-activated calcium channels which in turn causes excess neuronal excitability and further adds to misfolded proteins accumulation	Smith et al. (1992), Liu et al. (2004), and Samad et al. (2017)
Parkinson's disease	• Abnormal functioning of L-type calcium channels in substantia nigra pars compacta (SNc) dopaminergic neurons (DA) due to aging induced oxidative stress in nearby neurons causes increased influx of Ca2+ in these neurons • Increased calcium influx disturbs metabolic homeostasis of SNc DA leading to oxidative stress and DNA and mitochondrial damage • Increased oxidative stress causes increased production of proinflammatory cytokines which are released and recruit immune cells which destroy these DA recognizing them as abnormal • This leads to dopaminergic neuronal death in substanstia nigra	Tompkins et al. (1997), Calabrese et al. (2001), and Surmeier et al. (2010)
Clinical depression	• Aging causes low grade T-helper cells type-1 inflammation leading to release of inflammatory cytokines like interferon gamma, which transcriptionally induces the rate-limiting enzyme of tryptophan (Trp)-kynurenine (Kyn) pathway, indoleamine 2,3-deoxygenase (IDO) • Activation of IDO blocks Trp conversion to serotonin (substrate for antidepressant) and its derivatives: N-acetylserotonin (agonist to receptors of brain derived neurotropic factor), and melatonin (a pigment responsible for sleep regulation and circadian rhythms) • IDO activation leads to enhanced production of Kyn and its derivatives (anxiogenic, neurotoxic, and pro-oxidants), some of which upregulate nitric oxide synthase (NOS) • Increased activity of NOS leads to arginine metabolism to superoxide anions and other oxidative species leading to oxidative stress which exacerbate depression, anxiety and other cognitive impairments	Guidi et al. (1998), Oxenkrug (2011), and Costa et al. (2013)

effects, time of action, and proper dosage for the individuals over the age of 85. Hospitalization is considered as a normal practice amongst persons over the age of 85 mostly due to functional failure of the aged. As long as extensive acute care is taken at the home, older individuals can be saved from hospitalization and its difficulties like: further worsening of the condition due to iatrogenic infection. In order to avoid re-hospitalization, a routine medical checkup is important to minimize any errors that may lead to recurring disease manifestation (Singh 2016).

3.3 Types of Diseases Associated with Aging

3.3.1 Metabolic Diseases

3.3.1.1 Cardiovascular Diseases

Cardiovascular disease accounts for one of the most prevalent diseases in the older age. It affects the blood vessels and heart and is the leading cause of myocardial infarction (MI), coronary heart disease (CHD), and stroke. This disease is highly preventable if proper lifestyle measures are adopted, therefore reducing premature death ratio. In old age, a plethora of different conditions cause many diseases, similarly there has been a recent association of cardiovascular diseases with sensory impairments. A common mechanism of inflammation is implicated in both these conditions (Liljas 2017).

During the CVD, stiffness of the heart and blood vessels take place. This stiffness does not allow the arteries to carry more blood when pumped through the heart as a result causing increased blood pressure. This leads to an overall thickening of the heart muscle called hypertrophy (Jaul and Barron 2017). This makes it difficult for the heart to pump the blood, making physical activities more difficult as compared to that of a young heart. In CVD, the thickening of the capillary walls also takes place. This reduces the rate at which nutrients exchange takes place. The total volume of the blood also decreases, because there is a general reduction in total body water content as a person ages. In conditions of stress or illness, the pace at which red blood cell production takes place is lowered. Certain conditions that make the heart work harder include emotional stress, physical exertion, infections, and certain medicines (North and Sinclair 2012).

An overall change in the heart structure, with aging, leads to the formation of abnormal rhythms (arrhythmias) and are detected through ECG. Another common abnormality is the accumulation of lipofuscin—an aging pigment which is more common in the elderly. Because of stiffness of the heart valves, a certain disturbance in the heart sound is also observed called as the heart murmur. Apart from this, there are receptors in the blood vessels, called baroreceptors, these receptors help to normalize blood pressure. These receptors also undergo aging, which explains the reason of orthostatic hypotension in older people, a condition in which a person's blood pressure falls abruptly when a person goes from a lying position to standing or sitting (Strait and Lakatta 2012).

Common Problems Associated with Cardio Vascular Diseases (CVD)

- *Hardening of the arteries (Arteriosclerosis)*—fatty deposits in the blood vessels lead to this condition.
- *Angina* (a type of chest pain caused due to reduced flow of blood to the heart muscle).
- *Arrhythmias* (abnormal heart rhythm).
- *Anemia*—usually occurs due to nutritional deficits or chronic infections.
- High blood pressure/orthostatic hypotension.
- Deep vein thrombosis, blood clots, peripheral vascular disease, varicose veins are all manifestations of the CVD.
- In the older people, congestive heart failure is also very common.
- *Aortic stenosis* or the aortic valve is the most common valve disease in the elderly.
- *Aneurysms* may also develop in one of the major arteries from the heart or in the brain. They are caused by abnormal widening of the artery. If such an aneurysm bursts, it may lead to death.

3.3.1.2 Cerebrovascular Disease (Strokes)

Aging tend to bring about changes in the vascular endothelium and the arterial wall. According to recent studies, there is a reduction in vasodilatory capacity of the vascular endothelium. The arterial wall also undergoes changes due to calcium deposits and most importantly hypertrophy occurs that leads to an increase in vascular stiffness (Izzo et al. 2018).

Stroke is basically a vascular disease that directly affects brain and gives rise to a lot of manifestations. It is characterized by interrupted blood flow to the brain tissues due to breaking or closing of a cerebral artery. In the older adults, the prevalence is about 20–35%. In the western world, each year 10–12% deaths are caused due to stroke. Not only this, but it is also a leading cause of dementia and disability. Cerebral stroke tends to be a welfare issue, as the individuals are dependent upon others for their basic necessities (Gladyshev 2016). The protective function of the blood–brain barrier acts as a filter for the bloodstream in brain. As a person ages, the function of the BBB is distorted, the ability to selectively uptake nutrients is diminished. This in combination with inflammation like conditions leads to the formation of multi-infarct dementia (MID) and other neurodegenerative disorders (Farrall and Wardlaw 2009).

In the elderly population, the occasion of hemorrhagic events is more due a number of vascular structural changes like aneurisms, hypertension, increased cerebral trauma, amyloid deposits. It is quite evident from various studies that vascular dementia occurs in the older adults upon their exposure to a stroke or any hemorrhagic episode. In this type of dementia, the intellectual potential of a person is affected. The patients who are about 60, they are at a higher risk of experiencing a stroke associated vascular dementia, but here certain secondary conditions also exacerbate the disease, such as hypertension, diabetes, dyslipidaemias, etc. (Jaul and Barron 2017).

3.3.1.3 Hypertension

Another most common disease in the older adults is the hypertension which itself is the root cause of many other major diseases like atherosclerosis and CVD. However, its effects can be managed by bringing about positive changes in lifestyle and eating habits. Sedentary lifestyle and stress remains one of the prime causes for the diseases to persist and become severe (Logan 2011).

3.3.1.4 Bone and Joint Diseases

As aging proceeds bones become less dense, such moderate loss of bone density is called *osteopenia* and excessive loss of bone density is termed as *osteoporosis*. This excessive loss of bone density makes the bones become fragile and are susceptible to break even during a small accident. As estrogen (a female hormone) helps to main the bone density in women, upon menopause, less amount of estrogen results in further weakening of the bones (López-Otín et al. 2013).

Two other major factors that lead to the weakening of bones include reduction of calcium levels (as the body does not absorb maximum levels of calcium from dietary intake). Secondly, lower levels of Vitamin D further aggravate the disease. Some bones are more susceptible to weakening as compared to others. Most commonly affected bones include the spine bone, femur (thighbone), and radius and ulna (arm bones at wrist). As aging progresses, there are several changes taking place at the spine bone, which ends up in causing the head to slide forward which makes the throat compressed. This causes hard swallowing of food, and might as well result in occasional choking. The major reason that the older people become short is that their vertebra becomes dense and the tissues lose the lubricant fluid, making it thin and the spine becomes shorter (Jaul and Barron 2017).

Over the passage of time the joints become susceptible to injury because of many years of wear and tear. Such damage to the cartilage and use of joints leads to a condition called *osteoarthritis* which is the swelling and pain of joints. The joints of knee, hips, spine, and hands are usually affected. The elasticity of the ligaments which helps to bind the joints together is also lost with time and the tendons which binds muscle to bone also become less elastic. This as a result causes stiffness of joints and tissues weaken in the process contributing towards decrease flexibility and movements are altered while carrying on everyday tasks (Crimmins 2018).

3.3.1.5 Diabetes Mellitus

As people are becoming more and more overweight with increasing age, the diabetes rates are also increasing. The occurrence of diabetes amongst American adult population is likely to escalate more than 4 times by 2050. Cardiovascular diseases at the age of 85 are still influenced highly by Diabetes. Diabetes is also related directly to peripheral arterial disease and peripheral neuropathy, major contributing factor for diabetic foot ulcers and amputations. Every year around 6% and 0.5% of diabetic patients suffer from diabetic foot ulcers and amputations, respectively. Personalized management approaches are highly demanded in case of diabetes (Meneilly and Tessier 2001). Sulfonylureas and insulin transmit a considerable danger of hypoglycemia, therefore, the amount taken ought to be considered

cautiously in susceptible older adults. Dosing needs may vary for patients treated with hypoglycemic agents, especially during post-acute care or when patients are sent from hospital to home in uncertain periods. Frequent foot inspections are crucial for individuals with diabetes to avoid amputations. Blood circulation in the legs likely improves with regular walking (Jaul and Barron 2017).

3.3.1.6 Cancer

Cancer tends to be the second chief reason of death in elderly. Though, by the age of 85, the death ratio of cancer starts to decrease. Still, slow growing tumors appear to occur frequently for this age group. People respond to cancer treatment in accordance to their overall health status rather than their age. People in their 1980s or 1990s must not be deprived of intensive cancer treatment just because of their physical weaknesses (Robinson and Turner 2003).

Screening is not endorsed for breast cancer beyond 75 years, because of inadequate evidence for a possible outcome, although this might be useful for women with higher life expectancy. Likewise, for people above the age of 75 years, colon cancer screening is suggested merely in circumstances when there is an extensive life expectancy and a seemingly resilient ability to bear cancer diagnosis. Life expectancy is relatively flexible in elderlies at any age, established on the basis of comorbidities and other elements. Numerous false positives like identification of slow growing tumors forbid the screening for prostate cancer (López-Otín et al. 2013).

3.3.1.7 Chronic Obstructive Pulmonary Disease

Evidence suggests that aging and illnesses due to prolonged inflammation are closely related. Chronic Obstructive Pulmonary Disease (COPD) is a very slowly developing disease due to prolonged inflammation of the lungs, thus, most of the patients are aged. Aging characteristically is the consistent decay of homeostasis which happens once the reproductive phase of life is concluded, which leads to aggregated risk of disease. Non programmed aging, i.e. failure of organs to heal DNA destruction due to oxidative stress or programmed aging, i.e. shortening of telomere due to repeated cell division may cause the disease (López-Otín et al. 2013). Pulmonary function gradually declines with aging due to increased pulmonary inflammation, along with physical changes, inferred as senile emphysema. Ecological fumes, for instance, smoke of cigarette or various pollutants, may well hasten the aging of lungs by the formation of molecules such as histone deacetylases and sirtuins which subsequently prompts accelerated development of COPD (Gan et al. 2004).

3.3.1.8 Age-Related Macular Degradation

This disease affects the vision of the older adults. In this disease macula is affected, which is the part of retina where all nerve cells exist in close connection and therefore this is the region where the eye focusses the images that we observe. Therefore, this area is responsible for developing a clear and sharp focused image with fine details. The macula is affected as we age and it affects people over 65 years of age causing blindness or vision loss (Jaul and Barron 2017).

3.3.1.9 Blood Production

Aging declines the amount of active bone marrow cells, where new blood cells are formed. So, the blood cells production reduces. However, the bone marrow typically produces sufficient blood cells all the way till death. Issues may surface at a time where there is an increased requirement for blood cells, for example, during anemia, infection and/or severe bleeding happens. Under such conditions, when large amount of blood cells are needed at old age, bone marrow might show limited capacity to meet the higher blood cells demand (López-Otín et al. 2013).

3.3.1.10 The Immune System

The action of cells of the immune system retards with aging. Immune cells have a capacity to recognize and then remove foreign substances, for instance, bacteria, viruses, or cancer cells. Due to the reduction in the number of immune cells, certain manifestations occur in the aging adults as following (Gruver et al. 2007).

- Cancer is found commonly amongst older people.
- Older people are more frequently effected by some infections, for instance: influenza and pneumonia resulting more often in death. Moreover, vaccines seem to be less protective for older people though influenza, pneumonia, and shingles vaccines may provide some level of protection (Khan et al. 2017).
- Allergic symptoms are not very severe. Eventually, due to the poor performance of the immune system, autoimmune disorders are less likely to occur.

3.3.2 Psychological and Cognitive Diseases

3.3.2.1 Frailty Syndrome

Frailty is a very common clinical syndrome associated with increasing age and leads to health conditions like: falls, hospitalization, incident disability, and mortality. In theory, frailty is a clinically detectable state of amplified vulnerability caused by aging related decay in reserve and function across multiple physiologic systems so that the capacity to handle daily or acute stressors is compromised (Xue 2011). According to Fried et al. frailty is a condition where the body of an adult meet three out of five phenotypic conditions representing compromised energetics: (Fried et al. 2001)

- Low grip strength.
- Low energy.
- Slowed waking speed.
- Low physical activity.
- Unintentional weight loss.

Modern efforts on frailty have enhanced the level of understanding on the aging process and its possible biological connection. The operational definition of frailty, its domains either cognitive or physical and its correlation with aging, disabilities,

and prolonged sicknesses indicate that additional effort is required for improved understanding of frailty. Nonetheless, researchers and clinicians agree upon the strong effect of frailty on elder individuals, their caretakers and overall society. Though precise cures for frailty are still to be explored, the pre-existing medical methods offer convenient ways to identify prone people, which may lead to better treatment by keeping in view specific vulnerabilities and susceptibility for adverse health consequences (Xue 2011).

Regular exercising in order to strengthen the muscles can somehow delay loss of muscle mass and strength which contributes to frailty. On the contrary, being physically inactive, especially extensive bed rest during a disease, can significantly contribute to the muscle loss (Gladyshev 2016).

3.3.2.2 Cognitive Aging

By the age of 85, things like: difficulty in finding words, short-term memory loss, and slower processing of information are noticed quite often. Such regression in cognitive abilities can upset driving capabilities and may as well cause financial exploitation. Such manifestations can also lessen ability to cognize complex medical information. There is no uniform rate at which brain ages and typical cognitive aging may not lead to dementia. There are few functions like altruism, empathy, knowledge, and wisdom which generally increase with normal aging, giving the elderly a chance at society (Langa 2018).

3.3.2.3 Dementia

Chances of dementia rise with increasing age. Over the years, death toll from Alzheimer's disease have escalated than that for cardiovascular disease. The occurrence of dementia is estimated to increase to 131 million by 2050 over the globe. Even though dementia screening seems to possess inadequate clinical benefit as treatments are just marginally effective, however, provides alternates for improvement of public health. Several adults continue to live with dementia and might possibly be living precariously (Jaul and Barron 2017). The Folstein Mini-Mental State Examination though is frequently used tool to analyze dementia but it comprises numerous limitations. Individuals with dementia require chances for thinking incentive, caretaker's sustenance and perhaps evolved equipment to keep them safe (Waite 2018).

3.3.2.4 Dementia Including Alzheimer's Disease

In the USA, Alzheimer's disease is presently ranked to be the sixth foremost reason of death, however, recent assessments show that the disease may hike up to the third, after heart disease and cancer.

Dementia is most commonly caused by Alzheimer's in the elderly. Dementia is the loss of behavioral capabilities and cognitive activities like thinking, remembering, and reasoning so much so that it obstructs an individual's day-to-day life's activities. Severity of dementia may increase when it is mildly affecting a person's functioning,

to the most severe stage, where the person essentially depends on someone else even for the very basic chores of everyday life (Karantzoulis et al. 2011).

Numerous studies are being conducted to understand excessively about various biological traits of Alzheimer's. Progresses in brain imaging allows scientists to comprehend the growth and extent of atypical amyloid and tau proteins in the living brain, along with alterations in brain structure and functioning. Researchers are also determining the very primitive stages in the development of sickness by understanding deviations in the brain and body fluids which can be used to diagnose Alzheimer's symptoms before they actually surface (Langa 2018).

The question that why Alzheimer's occur in the elderly is yet to be answered. Researchers are trying to find relevant reasons as to how the changes occur with age inside the brain like: inflammatory actions, reduction of specific parts of the brain, mitochondrial malfunctioning, creation of unstable free radicals and vascular damage that may cause harm to the neurons and affect other brain cells leading to Alzheimer's disease (Karantzoulis et al. 2011).

3.3.2.5 Parkinson's Disease

Age is one of the most important players for the manifestation of Parkinson's disease (PD). The exact source of PD is yet unidentified, still the researchers rely on the fact that it results due to the amalgamation of some genetic and other external factors which are yet to be specified. PD disturbs numerous regions of brain and body. The death of neurons in brain region called the substantia nigra pars compacta and consequently reduced levels of dopamine are mostly accountable for motor symptoms like: shivering, stiffness, and loss of impulsive movement (Nussbaum and Ellis 2003). Investigations have revealed that the substantia nigra pars compacta displays high damage of neurons than other areas of the brain. Furthermore, with aging, organelles' become nonproductive leading to the accumulation of waste products that cannot be recycled and hence destroy the neurons (Reeve et al. 2014).

It is assessed that individuals with PD lose around 80% or even more of the dopaminergic neurons establish the motor symptoms. Consequently, over the time, the altered functioning of mitochondria and other organelles lead to the buildup of abnormal forms of alpha-synuclein which can possibly cause loss of neurons leading to motor symptoms (Jaul and Barron 2017).

3.3.2.6 Depression

Depression is not a standard outcome of aging. Sorrow may be some usual reaction to life activities that befall with aging like: grief, pensiveness, damage to cognition, social and/or physical attributes that lead to sickness. Major depression is common all the way through maturity but their occurrence rates decline between the age of 60 and 80, rising again after that. Occurrence of depression above the age of 85 is twice the rate between 70 and 74. Depression is more likely in the elderly who are confined to in old houses and the individuals with disabilities (Alexopoulos 2005).

Various approaches are implied for the diagnosis and treatment in order to reduce the amount of suffering, improve overall attitude of an individual, and lower the chances of suicide. Suicide rates amongst 85-year-old white Americans are extremely common.

3.4 Conclusion

The process of aging is universal but not the same in all the individuals. Various manifestation of aging, for example, decline in vision and auditory patterns, slow processing of information, lack of coordination can be addressed in a better way if proper awareness is created among the elderly. This would not only help the patients but also prepare the caretakers to manage all sorts of unforeseen problems.

Social and mental stressors are also a major cause of early aging. Timely addressal of these issues may prevent isolation, cognitive decline, and depression leading to suicide. Regular exercising should be a part of routine to strengthen the muscles and prevent disabilities during later life. Maintaining a balanced body weight by taking care of the diet may increase the total well-being of an individual as the incidence of diseases like osteoarthritis, diabetes, and CVD become less likely. People should be facilitated in such a way that in coming times, individuals over the age of 85 profit from home-based facilities and technologies along with innovative conveyance and housing facilities prospects for social contribution, plus plans to support family caregivers.

References

Ahuja N, Issa JPJ (2000) Aging, methylation and cancer. Histol Histopathol 15(3):835–842

Alexopoulos GS (2005) Depression in the elderly. Lancet 365(9475):1961–1970

Aravinthan AD, Alexander GJ (2016) Senescence in chronic liver disease: is the future in aging? J Hepatol 65(4):825–834

Aubert G, Lansdorp PM (2008) Telomeres and aging. Physiol Rev 88(2):557–579

Balatsouras D, Koukoutsis G, Fassolis A, Moukos A, Apris A (2018) Benign paroxysmal positional vertigo in the elderly: current insights. Clin Interv Aging 13:2251

Barnes PJ (2014) Cellular and molecular mechanisms of chronic obstructive pulmonary disease. Clin Chest Med 35(1):71–86

Barnes PJ (2016) Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 138(1):16–27

Bishop NA, Lu T, Yankner BA (2010) Neural mechanisms of ageing and cognitive decline. Nature 464(7288):529

Ble A, Cherubini A, Volpato S, Bartali B, Walston JD, Windham BG et al (2006) Lower plasma vitamin E levels are associated with the frailty syndrome: the InCHIANTI study. J Gerontol Ser A Biol Med Sci 61(3):278–283

Calabrese V, Scapagnini G, Stella AG, Bates TE, Clark JB (2001) Mitochondrial involvement in brain function and dysfunction: relevance to aging, neurodegenerative disorders and longevity. Neurochem Res 26(6):739–764

Cavazzana A, Röhrborn A, Garthus-Niegel S, Larsson M, Hummel T, Croy I (2018) Sensory-specific impairment among older people. An investigation using both sensory thresholds and subjective measures across the five senses. PLoS One 13(8):e0202969

Chen X, Mao G, Leng SX (2014) Frailty syndrome: an overview. Clin Interv Aging 9:433

Costa IC, Carvalho HN, Fernandes L (2013) Aging, circadian rhythms and depressive disorders: a review. Am J Neurodegener Dis 2(4):228

Crimmins E (2018) Trends in mortality, disease, and physiological status in the older population. In: Future directions for the demography of aging: proceedings of a workshop. National Academies Press, Washington

Davidson MB (1979) The effect of aging on carbohydrate metabolism: a review of the English literature and a practical approach to the diagnosis of diabetes mellitus in the elderly. Metabolism 28(6):688–705

Deary IJ, Corley J, Gow AJ, Harris SE, Houlihan LM, Marioni RE et al (2009) Age-associated cognitive decline. Br Med Bull 92(1):135–152

DeGroot J, Verzijl N, Wenting-Van Wijk MJ, Jacobs KM, Van El B, Van Roermund PM et al (2004) Accumulation of advanced glycation end products as a molecular mechanism for aging as a risk factor in osteoarthritis. Arthritis Rheum 50(4):1207–1215

Ergen AV, Goodell MA (2010) Mechanisms of hematopoietic stem cell aging. Exp Gerontol 45 (4):286–290

Faner R, Rojas M, MacNee W, Agusti A (2012) Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 186 (4):306–313

Farrall AJ, Wardlaw JM (2009) Blood–brain barrier: ageing and microvascular disease–systematic review and meta-analysis. Neurobiol Aging 30(3):337–352

Fine SL, Berger JW, Maguire MG, Ho AC (2000) Age-related macular degeneration. N Engl J Med 342(7):483–492

Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G (2001) Frailty in older adults: evidence for a phenotype. J Gerontol Ser A Biol Med Sci 56(3):M146–M157

Gan WQ, Man S, Senthilselvan A, Sin D (2004) Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 59 (7):574–580

Gemma C, Vila J, Bachstetter A, Bickford PC (2007) Chap. 15. Oxidative stress and the aging brain: from theory to prevention. In: Brain aging: models, methods, and mechanisms. CRC Press/Taylor & Francis, Boca Raton

Gladyshev VN (2016) Aging: progressive decline in fitness due to the rising deleteriome adjusted by genetic, environmental, and stochastic processes. Aging Cell 15(4):594–602

Greene MA, Loeser RF (2015) Aging-related inflammation in osteoarthritis. Osteoarthr Cartil 23 (11):1966–1971

Gruver A, Hudson L, Sempowski G (2007) Immunosenescence of ageing. J Pathol 211(2):144–156

Guarner V, Rubio-Ruiz ME (2015) Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. In: Aging and health—a systems biology perspective, vol 40. Karger Publishers, Basel, pp 99–106

Guidi L, Tricerri A, Frasca D, Vangeli M, Errani AR, Bartoloni C (1998) Psychoneuroimmunology and aging. Gerontology 44(5):247–261

Haas RH (2019) Mitochondrial dysfunction in aging and diseases of aging. Multidisciplinary Digital Publishing Institute, Basel

Hajjar ER, Cafiero AC, Hanlon JT (2007) Polypharmacy in elderly patients. Am J Geriatr Pharmacother 5(4):345–351

Hakim FT, Flomerfelt FA, Boyiadzis M, Gress RE (2004) Aging, immunity and cancer. Curr Opin Immunol 16(2):151–156

Hall JA, Dominy JE, Lee Y, Puigserver P (2013) The sirtuin family's role in aging and age-associated pathologies. J Clin Invest 123(3):973–979

Hamerman D (1993) Aging and osteoarthritis: basic mechanisms. J Am Geriatr Soc 41(7):760–770
Harman D (1992) Free radical theory of aging: history. In: Free radicals and aging. Birkhäuser, Basel, pp 1–10
Harvey A, Montezano AC, Lopes RA, Rios F, Touyz RM (2016) Vascular fibrosis in aging and hypertension: molecular mechanisms and clinical implications. Can J Cardiol 32(5):659–668
Hirai T, Korogi Y, Sakamoto Y, Hamatake S, Ikushima I, Takahashi M (1996) T2 shortening in the motor cortex: effect of aging and cerebrovascular diseases. Radiology 199(3):799–803
Huang Q, Tang J (2010) Age-related hearing loss or presbycusis. Eur Arch Otorhinolaryngol 267 (8):1179–1191
Izzo C, Carrizzo A, Alfano A, Virtuoso N, Capunzo M, Calabrese M, De Simone E, Sciarretta S, Frati G, Oliveti M (2018) The impact of aging on cardio and cerebrovascular diseases. Int J Mol Sci 19(2):481
Jang JY, Blum A, Liu J, Finkel T (2018) The role of mitochondria in aging. J Clin Invest 128 (9):3662
Jaul E, Barron J (2017) Age-related diseases and clinical and public health implications for the 85 years old and over population. Front Public Health 5:335
Jun T, ke-yan F, Catalano M (1996) Increased superoxide anion production in humans: a possible mechanism for the pathogenesis of hypertension. J Hum Hypertens 10(5):305–309
Karantzoulis S, Galvin JE, Braak, Salmon, Mckhann, McKhann, Jack, Sperling, Hodges, Butters (2011) Distinguishing Alzheimer's disease from other major forms of dementia. Expert Rev Neurother 11(11):1579–1591
Khan SS, Singer BD, Vaughan DE (2017) Molecular and physiological manifestations and measurement of aging in humans. Aging Cell 16(4):624–633
Kim H, Kisseleva T, Brenner DA (2015) Aging and liver disease. Curr Opin Gastroenterol 31 (3):184
Kinnunen K, Petrovski G, Moe MC, Berta A, Kaarniranta K (2012) Molecular mechanisms of retinal pigment epithelium damage and development of age-related macular degeneration. Acta Ophthalmol 90(4):299–309
Langa KM (2018) Cognitive aging, dementia, and the future of an aging population. In: Future directions for the demography of aging: proceedings of a workshop. National Academies Press, Washington
Liljas AEM (2017) The relationship of sensory impairments with cardiovascular disease and mortality, disability and frailty in older age: longitudinal cohort studies using the British Regional Heart Study and the English Longitudinal Study of Ageing, UCL (University College London)
Liu H, Wang H, Shenvi S, Hagen TM, Liu RM (2004) Glutathione metabolism during aging and in Alzheimer disease. Ann N Y Acad Sci 1019(1):346–349
Logan AG (2011) Hypertension in aging patients. Expert Rev Cardiovasc Ther 9(1):113–120
López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153(6):1194–1217
Manolagas SC (2000) Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev 21(2):115–137
Manolagas SC (2010) From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. Endocr Rev 31(3):266–300
McGuire PJ (2019) Mitochondrial dysfunction and the aging immune system. Biology 8(2):26
Meneilly GS, Tessier D (2001) Diabetes in elderly adults. J Gerontol Ser A Biol Med Sci 56(1):M5–M13
Morley JE (2008) Diabetes and aging: epidemiologic overview. Clin Geriatr Med 24(3):395–405
Naor D, Bonavida B, Walford RL (1976) Autoimmunity and aging: the age-related response of mice of a long-lived strain to trinitrophenylated syngeneic mouse red blood cells. J Immunol 117(6):2204–2208
North BJ, Sinclair DA (2012) The intersection between aging and cardiovascular disease. Circ Res 110(8):1097–1108

Nussbaum RL, Ellis CE (2003) Alzheimer's disease and Parkinson's disease. N Engl J Med 348 (14):1356–1364
Oxenkrug G (2011) Interferon-gamma–inducible inflammation: contribution to aging and aging-associated psychiatric disorders. Aging Dis 2(6):474
Palmer AK, Kirkland JL (2016) Aging and adipose tissue: potential interventions for diabetes and regenerative medicine. Exp Gerontol 86:97–105
Patyar S, Prakash A, Modi M, Medhi B (2011) Role of vinpocetine in cerebrovascular diseases. Pharmacol Rep 63(3):618–628
Prelog M (2006) Aging of the immune system: a risk factor for autoimmunity? Autoimmun Rev 5 (2):136–139
Reeve A, Simcox E, Turnbull D (2014) Ageing and Parkinson's disease: why is advancing age the biggest risk factor? Ageing Res Rev 14:19–30
Rickman CB, Farsiu S, Toth CA, Klingeborn M (2013) Dry age-related macular degeneration: mechanisms, therapeutic targets, and imaging. Invest Ophthalmol Vis Sci 54(14):ORSF68–ORSF80
Riggs BL, Khosla S, Melton LJ III (1998) A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res 13(5):763–773
Roberts KL, Allen HA (2016) Perception and cognition in the ageing brain: a brief review of the short-and long-term links between perceptual and cognitive decline. Front Aging Neurosci 8:39
Robinson JD, Turner J (2003) Impersonal, interpersonal, and hyperpersonal social support: cancer and older adults. Health Commun 15(2):227–234
Sahoo S, Meijles DN, Pagano PJ (2016) NADPH oxidases: key modulators in aging and age-related cardiovascular diseases? Clin Sci 130(5):317–335
Samad N, Ishaq S, Bano S, Manzoor N (2017) Calcium regulation in Alzheimer's disease: mechanistic understanding. J Coll Physicians Surg Pak 27(9):566–571
Saretzki G, von Zglinicki T (2002) Replicative aging, telomeres, and oxidative stress. Ann N Y Acad Sci 959(1):24–29
Sarkar D, Fisher PB (2006) Molecular mechanisms of aging-associated inflammation. Cancer Lett 236(1):13–23
Shaffer SW, Harrison AL (2007) Aging of the somatosensory system: a translational perspective. Phys Ther 87(2):193–207
Shammas MA (2011) Telomeres, lifestyle, cancer, and aging. Curr Opin Clin Nutr Metab Care 14 (1):28
Shay JW (2016) Role of telomeres and telomerase in aging and cancer. Cancer Discov 6 (6):584–593
Shay JW, Wright WE (2001) Telomeres and telomerase: implications for cancer and aging. Radiat Res 155(1):188–193
Sheedfar F, Biase SD, Koonen D, Vinciguerra M (2013) Liver diseases and aging: friends or foes? Aging Cell 12(6):950–954
Simmonds MJ, Meiselman HJ, Baskurt OK (2013) Blood rheology and aging. J Geriatr Cardiol 10 (3):291
Singh I (2016) Assessment and management of older people in the general hospital setting. In: Challenges in elder care. InTech, London, p 37
Smith CD, Carney JM, Tatsumo T, Stadtman ER, Floyd RA, Markesbery WR (1992) Protein oxidation in aging brain a: protein oxidation in aging brain. Ann N Y Acad Sci 663(1):110–119
Strait JB, Lakatta EG (2012) Aging-associated cardiovascular changes and their relationship to heart failure. Heart Fail Clin 8(1):143–164
Stuen C, Faye E (2003) Vision loss: normal and not normal changes among older adults. Generations 27(1):8–14
Surmeier DJ, Guzman JN, Sanchez-Padilla J (2010) Calcium, cellular aging, and selective neuronal vulnerability in Parkinson's disease. Cell Calcium 47(2):175–182

Taddei S, Virdis A, Ghiadoni L, Versari D, Salvetti A (2006) Endothelium, aging, and hypertension. Curr Hypertens Rep 8(1):84–89

Terrando, N., Brzezinski, M., Degos, V., Eriksson, L. I., Kramer, J. H., Leung, J. M., et al. (2011). "Perioperative cognitive decline in the aging population." Mayo Clinic proceedings, Elsevier, Amsterdam 86(9): 885-893.

Tompkins MM, Basgall EJ, Zamrini E, Hill WD (1997) Apoptotic-like changes in Lewy-body-associated disorders and normal aging in substantia nigral neurons. Am J Pathol 150(1):119

Topinková E (2008) Aging, disability and frailty. Ann Nutr Metab 52(Suppl. 1):6–11

Vlassara H (1996) Protein glycation in the kidney: role in diabetes and aging. Kidney Int 49 (6):1795–1804

Waite LJ (2018) Social well-being and health in the older population: moving beyond social relationships. In: Future directions for the demography of aging: proceedings of a workshop. National Academies Press, Washington

Wang JC, Bennett M (2012) Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. Circ Res 111(2):245–259

Wang J, Ohno-Matsui K, Morita I (2012) Elevated amyloid β production in senescent retinal pigment epithelium, a possible mechanism of subretinal deposition of amyloid β in age-related macular degeneration. Biochem Biophys Res Commun 423(1):73–78

Weyand CM, Goronzy JJ (2016) Aging of the immune system. Mechanisms and therapeutic targets. Ann Am Thorac Soc 13(5):S422–S428

Xia S, Zhang X, Zheng S, Khanabdali R, Kalionis B, Wu J et al (2016) An update on inflamm-aging: mechanisms, prevention, and treatment. J Immunol Res 2016:1

Xue Q-L (2011) The frailty syndrome: definition and natural history. Clin Geriatr Med 27(1):1–15

Yan J, Zhang H, Yin Y, Li J, Tang Y, Purkayastha S et al (2014) Obesity-and aging-induced excess of central transforming growth factor-β potentiates diabetic development via an RNA stress response. Nat Med 20(9):1001

Yang Z, Ming XF (2012) mTOR signalling: the molecular interface connecting metabolic stress, aging and cardiovascular diseases. Obes Rev 13:58–68

Yin D, Chen K (2005) The essential mechanisms of aging: irreparable damage accumulation of biochemical side-reactions. Exp Gerontol 40(6):455–465