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Physiologic Changes in The Elderly

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Abstract:

As the older population has been tremendously growing, the physiologic changes of all organ systems in increasing age should be extensively recognized. The changes include the increased risk of myocardial infarction or hypertension in cardiovascular system, respiratory failure in respiratory system, malignant melanoma in aging skin. The impaired coordination of muscles of swallowing also increases risk of aspiration. In addition, the immune system with altered function slows down the inflammation process of the body, leading to atypical presentation when the patient is acute illness. In this article, aging changes of organ systems and the potentially altered risk of diseases including the pharmacokinetic and pharmacodynamic changes in the elderly are described for the benefit of patient care.

Keywords: Physiology, Change, Elderly, Aging

Introduction

Nowadays, birth rate is declining in spite of increasing human life span. Trends of elderly populations growth occur in several countries especially in Europe and Asia.[1] Aging societies, according to United Nation, defined as the share of population aged more than 65 are exceed 7 percent of whole population in the country[2], going to pace all around the world. These global changes challenge social and family welfare system, economic systems and health care systems.[3] Aging is a natural process that occurs from accumulation of changes in any organ system, either function or number of cells and tissues. This changing process leads to progressive increasing the risk of disease and death.[3] These changes create the different perspectives of diseases between adults and elderly including epidemiology, characteristics, prognosis, complications and limitations of treatment. Therefore, physicians and healthcare workers need to know about changing in the organ system to increase their capability to treat and care elderly patients.

Theory of aging process

Currently, the process of aging is still questionable. Multiple theories were launched but were still controversial and unproved.[4,5] Generally, the process of aging is divided into intrinsic and extrinsic causes. The extrinsic causes or so-called "stochastic" are hypothesized that cumulative exposed

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of free radicals and radiation lead to cellular damage, error in protein synthesis and degradation of protein cross-linking. The intrinsic causes or "Developmental-genetic theories" are explained that there are preprogrammed, genetic controls which affect dynamic transformation of intracellular organ systems and erode homeostasis in adulthood after maturation is complete.[6,7]

Homeostenosis

Homeostenosis is the body phenomenon that decreases the ability to maintain balances of organ function under stress. Everybody is given excess capacity in organ and biologic systems called "physiologic reserve" at birth. This reserve is used to buffer any stress such as illness, trauma to maintain homeostasis. As time goes by, this reserve declines, and then aging body reduces capacity to endure any injury to organ systems. If the stress is over body reserve, it can cause disease, decompensation and death.[8,9] Figure 1 shows homeostenosis which means progressively reducing of body reserve according to increasing age and the attack of stress such as illness. At the end of the curve shows sharp decline, that means at the very end stages of life or very elderly, body reserves are easily reduced and lead to death when the stress comes out. This progressively body reserve declining definitely as "deconditioning" or "frail." [10]

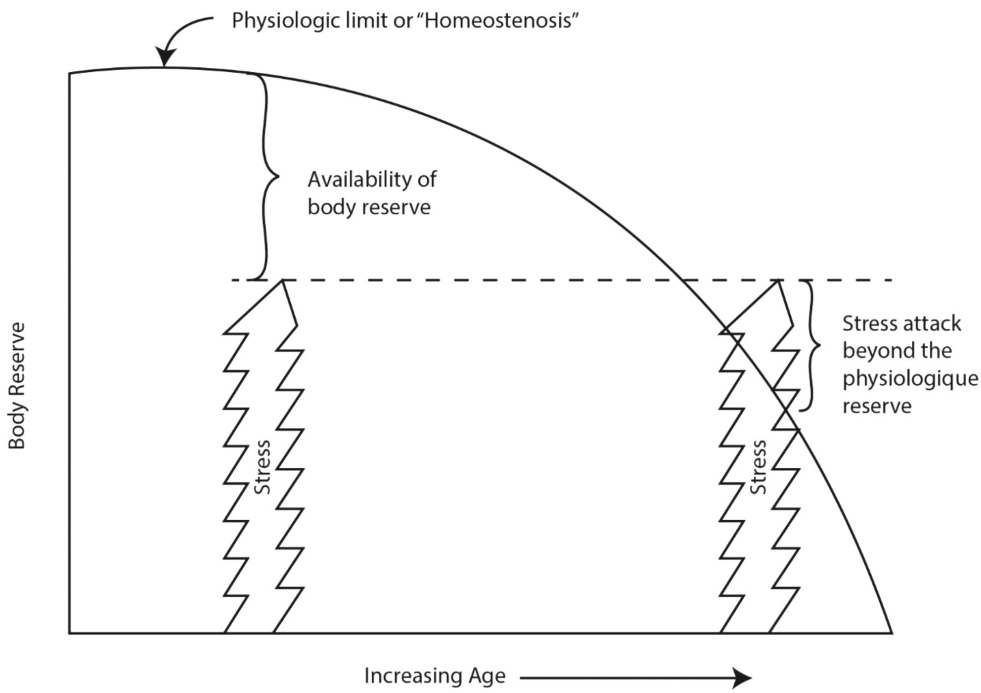

Figure1 Natural process of. homeostenosis Body composition

In the elderly, the body composition changes along aging process. Many studies show that body weight and body mass index (BMI) do not change significantly but fat mass is increased and muscle mass is decreased.[11,12] This changing process effects pharmacokinetics of the elderly then has a consequence of medical treatment of any disease in the elderly.

Theoretically, plasma protein binding and fat body mass affects drug volume distribution. Drugs with lower plasma protein binding capacities have higher volume of distribution, less plasma drug

concentration and drug toxicity. "Lipophilic drugs" refer to drugs that have high solubilities to fatty tissue, they have more capabilities to distribute drug level in extravascular tissues (Vd) than "Hydrophilic or water-soluble drugs". On the other hand, hydrophilic drugs have higher potency to concentrate in plasma volume.[13]

As aging changed, fatty mass is increased that effected the volume distribution of any drugs. Lipophilic drugs such as diazepam, thiopentone, fluoroquinolones, macrolides have more distribution of extravascular tissue (Vd) which leads to prolong half-life and accumulation of drugs. Therefore, the frequency of administration of these drugs should be monitored. In contrast, total body water in the elderly tends to be decreased, so highly water-soluble drugs or hydrophilic drugs have higher drug plasma concentrations. Hence, drug toxicity easily occurs in the elderly especially using hydrophilic drugs such as digoxin, aminoglycosides, penicillin, theophylline. All these phenomena explain why physicians should be aware when prescribing any drugs in elderly patients and have to "start low and go slow" during titration of drug dosages to achieve the most potency and least toxicity.

Skin and musculoskeletal system

Skin is the largest organ of the body that includes an area of about 20 square feet and is anatomically classified as 3 parts: epidermis, dermis and hypodermis. All parts have degenerative aging changes resulting in higher risk for skin disease than the normal population.

Epidermis and dermis become thinner. Dermoepidermal junction flattens and loss undulation. Vessel walls are also thinner. These changes increase the fragility of skin when applied with shearing stress. The skin becomes more transparent and easily bruising. Other that, thin skin is at risk of irritation and leading to wound such as skin that has been exposed to urine or feces.

Distribution of vascularity, fibroblast, fat tissue and collagen are also decreased. Hence, healing process is delayed in the elderly when they have trauma. Importantly, skin is one of protective barrier to any infections then elderly have higher susceptibility to skin infections than young adults.

The declining number of sweat glands makes skin drier and leads to higher risk of xerotic dermatitis, seborrheic dermatitis in the elderly. The number of Meissner's corpuscles and Pacinian corpuscles, which are sensory receptor, also decreased. Consequently, the elderly has less pain sensation and proprioception than young adults leading to higher risk of trauma, wound and falling.

The aging body has a change of keratinocytes, melanocytes, fibroblasts and endothelial cells. These changes cause the skin to grow when exposed to UV light and develop abnormal keratin and melanin growth, leading to skin malignancy such as actinic keratosis and melanoma.[14]

A decrease in the amount of keratinocytes and subdermal fat results in a wrinkle. The wrinkle itself affects UV exposure. An aged wrinkle is characterized by thin, finely and dry wrinkle, while photoaging or UV exposure skin appears. They are more likely to be deep, rough and lax wrinkle.[15]

According to musculoskeletal, the decreased amount of muscle mass leading to higher risk of sarcopenia. The definition of sarcopenia, according to The European Working Group on Sarcopenia in Older People (EWGSOP)[16] is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength and/or physical performance, associated with a risk of adverse outcomes such as physical disability, poor quality of life, and death. Muscle is a type of protein, therefore, when the amount of muscle is reduced, it may alter the pharmacodynamic effect of the drug-binding protein.

The aging body also reduces production of osteoblast, while osteoclast numbers remain unchanged.17 Meanwhile, 7-dehydrocholesterol production in the epidermal layer is decreased, the amount of vitamin D is increased, which attenuate calcium absorption[18] leading to osteopenia or osteoporosis and pathologic fracture in the elderly which subsequently increase morbidity and mortality.

Cardiovascular system

There are changing in endothelial wall; increased intimal thickness, vascular smooth muscle hypertrophy, fragmentation of the internal elastic membrane and an increase in the amount of collagen and collagen cross-linking in arterial walls, which may attribute to increasing afterload, systolic blood pressure and widening pulse pressure. Over the long term, ventricular hypertrophy can occur in the elderly.

Moreover, the thickening of the endothelium leads to impair endothelium dependent-vasodilatation. When the body needs more cardiac output, such as during exercising or acute illness, the body is unable to dilate the blood vessel to enhance blood flow for the increased demand of total organ system. This leads to increase risk of cardiac ischemia, coronary artery disease and peripheral vascular disease.[19]

Cardiovagal baroreflex sensitivity decreased which may induce several consequences including increased levels of BP variability, higher potency of orthostatic hypotension, an impaired ability to respond to acute challenges to the maintenance of BP, and increased risk of sudden cardiac death.[20]

From above, the arterial stiffness results in ventricular hypertrophy which make the ventricle thickening, but the ventricular mass is not clearly altered. Such age changes result in decreased end-diastolic volume, but the systolic volume remains unchanged. This leads to a decrease in myocardial relaxation and myocardial compliance, therefore the elderly is at higher risk of developing diastolic dysfunction or diastolic heart failure than young adult.[19]

In addition, myocardium has loss of myocytes, the cause of which myocytes loss is currently unknown. It was also found that there was a decrease in capillary density, both of which increased the likelihood of myocardial ischemia more easily with increasing age.[21]

Whilst both β adrenergic receptor density and the ratio of β1 to β2 receptors do not change with aging, senescent myocytes show a decreased responsiveness to β adrenergic stimulation.[22] As a result, the body is unable to drive maximum heart rate or maximum cardiac output according to stimuli or stress such as exercise, infection or shock. When the body fails to increase cardiac output, in case of increasing cardiac demand occur, this can lead to pumping failure or pulmonary edema. Other than that, the decreased responsiveness to β receptor can cause adverse effects easier than young adult when expose to beta-blocker drugs such as bradycardia or hypertension.

In addition to the change in the structure of the blood vessel and myocardium in the elderly, the autonomic regulation of heart also changes over time. According to Kuga K. et. al, the parasympathetic tone of sinus node functions is decreased, along with the conduction time of the sinus node. Study also shows that atrioventricular node is prolonged as the age increased.[23] This puts the elderly at higher risk of heart block such as sick sinus syndrome, AV block or bundle branch block than young adult.

Respiratory system

In the elderly, there are changes in the respiratory system, both in terms of structure and lung mechanics, which may not be noticeable change in normal conditions. But it results in the elderly having higher potency of respiratory failure when they have acute illness or respiratory infection. Therefore, the elderly has higher risk of intubation, prolong ventilator, longer hospitalization, morbidity and mortality outcome.

For structural changes, chest wall in elderly become stiffer. The anterior and posterior diameters of the thoracic cage change to be more likely round shape. Skeletal muscle of breathing has loose strength.[24,25] The lung parenchyma loses elasticity, causing the elastic recoil to deteriorate. In addition, the small airway has less elasticity and the airway caliber decreases. All of the changes result in decreased lung compliance and the elderly would require more effort to breathe and increase the chance of small airway obstruction more easily than young adult.

Cilia which function in the mucocilliary clearance of sweeping mucus and dirt out of the lungs[26] become slower with age. This aging change causes reduced capacity to get rid of secretion or germs like bacteria or virus from the lungs. Together with respiratory muscle atrophy with age, the elderly has decreased effort to cough to get rid of secretion. All of these put the elderly at higher risk of pneumonia and secretion obstruction.[25]

On the lung mechanics aspect of the elderly, decrease in elastic recoil and lung compliance causes reduction of the 1-second force expiratory volume (FEV1) and forced vital capacity (FVC). Study of B. Burrows et al. found that FEV1 decreased by approximately 35 mL/year, but this reduction was not directly proportional to the linear curve and found that men had a higher rate of reduction than women.[27]

Total lung capacity (TLC) in the elderly does not change with age and tidal volume remains the same. However, due to stiffer chest wall and loose respiratory muscle function, the elderly has decreased inspiratory reserve volume (IRV) and expiratory reserve volume (ERV), resulting in decreased vital capacity and increased lung residual volume. Force residual capacity (FRC) remains unchanged.[28]

Because of the increased airway resistance due to the smaller size of small airway caliber in aging change and decreasing elasticity of airway when the peak expiratory flow rate was examined, it was found to decrease with increasing age. [25,28]

Although, Force vital capacity and tidal volume decreases, minute ventilation of the elderly in resting state is not different from adulthood. Hence, it has compensation that respiratory rate should be increased. During physical exertion or stress that require an increased minute volume, these situations increase the likelihood shortness of breath and increase risk of respiratory failure especially when the elderly has acute illness.

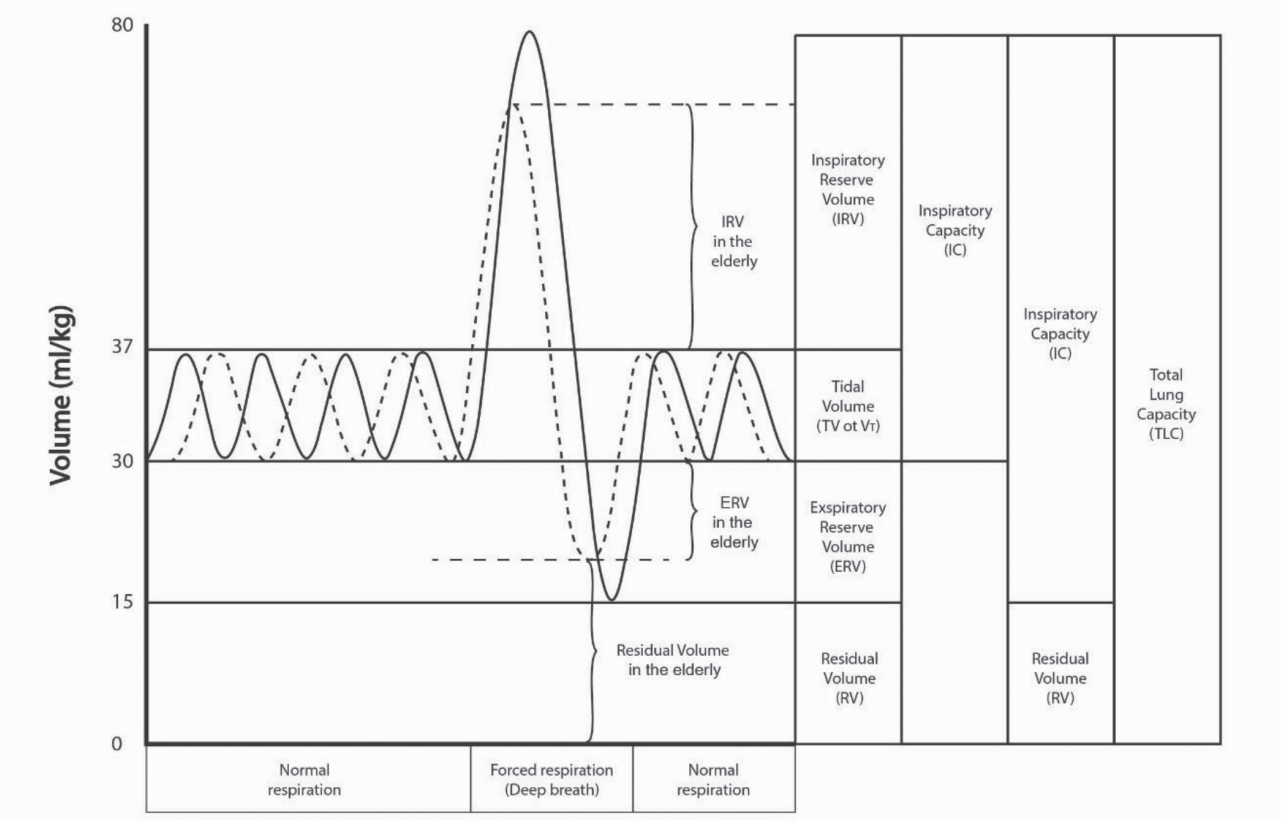

Figure 2 Schematic aging-response of lung mechanics[29]

Related to aging, the body's vessel thickens, and the lungs have more dead space and the alveolar-capillary membrane thickens. All these changes increase the chances of ventilation-perfusion imbalance.

According to H. Stam et.al study, the diffusion capacity for carbon monoxide (DLCO) was decreased with age by 0.2 mL CO/min/mmHg/year in men and by 0.15 mL CO/min/mmHg/year in women.[30]

Hypercapnic and hypoxic response were also declined with aging which resulted in no symptom or delayed response to hypoxemia or hypercapnia, presumably atypical presentation in the presence of pulmonary disease.

Gastrointestinal system

The changes are described according to anatomy as follows:

1. Oropharyngeal part

Oral epithelial mucosa is thinner and enamel production is reduced. Together with the gums are more receding. All these things make the teeth easily decayed and eroded. The function of orobuccal muscle is reduced. Some elderly who have so many dental caries or dental loss, that the number of teeth is less than 20, they are unable to close their mouth completely.

The coordination of the oropharyngeal muscles and the swallowing reflex are impaired, making it impossible to combine food into a food bolus before swallowing. Besides that, the coordination of swallowing muscle is not related to the amount of food eaten. This causes the higher risk of aspiration and leads to higher risk of aspiration pneumonia in the elderly.[30]

Additionally, the protein content of saliva changes, but the saliva flow rate remains the same. As a result of taking a variety of drugs, the elderly has higher potency to be xerostomia.[31]

According to Whelan et. Al. study, microbial population in the oropharynx in

elderly was changed in quantity and type of microbiome, therefore, immune defense from microbiome was different from adult, and led to higher risk for respiratory tract infection.[32]

2. Esophageal part

Loss of esophageal compliance, resulting in swallowing dysfunction, increases the risk of esophageal reflux and aspiration pneumonia.[33]

3. Stomach and intestinal part

In the stomach, there is a decrease in the amount of intestinal Cajal body. The Cajal body acts as a pacemaker, sending slow wave potential to the intestinal smooth muscle causing intestinal contraction. As the number of Cajal bodies decreases, the gastric emptying time and intestinal transit time are slowed down. Hence, the elderly eats less, causing anorexia due to indigestion and constipation. Moreover, the drug effect is slower due to longer transit times.[34,35]

Prostaglandins are unsaturated fatty acids and act as protective barrier of gastric mucosa from any irritants. In the elderly, there was a decrease in the amount of prostaglandins production. Therefore, the secretion of bicarbonate in the stomach is decreased, while parietal cells secretion of hydrochloric acid is the same, increasing the risk of gastritis or gastric ulcer.[36]

Due to the thickening of the vessel, the mesenteric, splanchnic and gastric blood flow is reduced, especially after meals. The body undergoes splanchnic blood pooling without compensation from the peripheral vascular system, resulting in postprandial hypotension which is one of the most common causes of syncope in the elderly.[37,38]

4. Hepatobiliary system

In the elderly, liver mass, liver perfusion, and liver blood flow are decreased while mitochondrial integrity and enzymatic activity remain unchanged.

Due to decreased hepatocyte, hepatic oxygen diffusion and liver blood flow, study of Anantharaju et.al. has shown that hepatic drug metabolism by cytochrome P450 is also reduced resulting in changes in pharmacokinetics, especially in the first part drug metabolism. Therefore, some drugs have a longer duration in the elderly and should be avoided such as benzodiazepines or some antihypertensive drugs.[39]

According to Le Coutour et.al., a decrease in hepatic perfusion affects hepatic drug clearance. If the elderly need to take the drugs with high clearance activity, the dose should be reduced by 40%, while with the low clearance drug should be reduced by 30%. Otherwise, drug toxicity may occur.[40]

Genitourinary system

With increasing age, there are structural, hemodynamic and physiologic changes of the kidney. Total nephron size and number are decreased. There are thickening of basement membrane, glomerulosclerosis, tubular atrophy and interstitial fibrosis.[41]

A decrease in the number of functional nephrons is associated with a decrease in glomerular filtration rate. The glomerular filtration rate begins decreasing 1mL/min/1.73 m^2/year, starting at 30 years of age. But the decreasing rate can change if other factors are affected, such as hypertension or drug toxicity, etc.[42,43]

Glomerulosclerosis contributing to hypertension in the elderly, but in various studies, there was no association with age-related declines in glomerular filtration rate.[40]

From these changes, when people get older, the number of function-preserved nephrons is reduced. So, the elderly has higher risk of acute kidney injury than young adults, especially when certain factors are affected, including acute illness, nephrotoxic drugs, atherosclerosis, etc.

For the lower urinary tract, a study by S. Madersbacher et.al. found that elderly

had significant decreased bladder capacity, average and peak urine flow rate, urinary voided volume but increased post-void residual volume.[44] All these changes make the elderly have frequency of urination and nocturia.

In elderly women, a significant decrease in functional urethral length and maximum urethral closing pressure puts them at an increasing risk of urinary incontinence and subsequent urinary tract infection.

On the contrary, elderly men are found that prostate volume increases which make the high likelihood of benign prostatic hypertrophy, urinary tract obstruction and urinary tract infection.

For female reproductive system, after menopause, there are changes of hypothalamic-pituitary-ovarian axis leading to atrophy of uterus, ovary, fallopian tube and vagina, reduction of cervical and vaginal secretion. All these changes increase risk of atrophic vaginitis in the elderly.

On the other hand, aging male reproductive system has effect of changing in hypothalamic-pituitary-gonadal axis too but their function is sufficient to maintain fertility in elderly men, except minimal change in sperm motility, quality and quantity.[45]

Nervous system

Related to peripheral nervous system, the β-receptor number is decreased and the response to the receptor is also decreased in the elderly. While the α adrenergic response remains normal, it does not change with age. Baroreceptor response also decreases resulting in a higher chance of beta-blocker side effects which is bradycardia and syncope than young adults.[46]

In the part of the autonomic nervous system, sympathetic overactivity is more common in the elderly while muscarinic parasympathetic activity was declined.[46]

All these changes affect the body as a whole, whether blood pressure, heart rate response to stress, cerebral blood flow or bladder activity. These increase potency of hypertension, coronary heart disease, syncope, incontinence or urinary tract obstruction, and also, change the efficacy of anticholinergic drug responsiveness.

In the aging brain, there are some losses of synaptic contacts and neuronal apoptosis that provoke age-dependent declines in sensory processing, motor performance and cognitive function. [47] The brain shrinks in volume, particularly in the frontal cortex.[48]

The shrinkage brain and synaptic loss cause memory decline in the elderly and increase risk of neurodegenerative diseases such as Alzheimer's disease, vascular dementia, etc. In normal elderly, their episodic memory function does not decline but it takes longer to recall. Multitasking and locomotive motor speeds are slower or disrupted when compared to young adult. Learning ability takes longer and more repetition than adult. Working memory or "skill" still intact when getting older. Finally, judgement and decision-making, known as "executive function", is still the same as always.[49]

Hematologic and immune system

In the elderly, bone marrow changes cellularity like every organ system. The percentage of hematopoietic cells that occupy bone marrow decreased from 40-60% in young adults to 20-40%. The remaining space is occupied by fat. However, sufficient stem cell proliferation and maturation is still preserved. Hence, the preserved transferred stem cells remain capable of normal hematopoiesis throughout entire life. Peripheral blood counts and parameters are kept unchanged.[50]

According to Davy Kevin P. et.al, total blood volume, plasma volume and

erythrocyte volume are significantly lower than in young adults.[51] These aging changes increase the tendency to anemia in the elderly, either from blood loss, nutritional anemia or myelodysplastic syndrome.

The immune response becomes altered as aging changes, called "immunosenescence". Immune response is classified as innate and adaptive immunity. The innate immune system has important components, phagocytes, which are the first barrier aggregated to eliminate aggression of bacteria and fungi, and neutrophils which have specific receptors (FMLP, GM-CSF, IL-8) to combat pathogen. Some studies show that phagocytosis and neutrophil function do not change with age but specific receptors decline signal function and chemotaxis leading to slower and less response to infection and inflammation in old age than young adults.[52]

Adaptive immunity has higher specificity to each particular pathogen than the innate immune system. Besides, adaptive immunity creates an immunological memory after an initial response to a specific pathogen and then produces an "antibody" which lasts long protection. This process also forms the basis of vaccination. T-cells and B-cells are the main components of adaptive immunity. Immunosenescence of aging reduces ability to accumulate T-cells, and decreases the output of naïve T-cells. Whereas, B-cells even decrease in number that leads to decreased secretion of immunoglobulin, they also shift antibody from foreign antigen to autologous antigen. All the changing process make elderly lower immunity to infection, lower expression of inflammation, higher risk of autoimmune disease and lower activity of vaccination.[53,54]

According to Wilkerson W.R. et.al study, the elderly was found to have increased fibrinogen, factor VIII, IX and coagulation proteins. This associates with dramatic increasing rate of arterial and venous thrombosis, like stroke, myocardial infarction and pulmonary embolism.[55]

Endocrine system

Like all other organ systems, the endocrine system undergoes age-related changes but the systems that are affected directly in the elderly and may need treatment are thyroid hormone and insulin secretion of the pancreas.

Aging changes of the thyroid involve thyroid hormone production, metabolism and action. There is an overall decrease secretion of TSH from the pituitary, T3 and T4 from thyroid gland but the distribution of TSH relatively tends to shift upward with aging. Therefore, prevalence of biochemical subclinical hypothyroidism is higher in the elderly.

Besides that, chronic diseases (such as chronic obstructive lung disease, arthritis) and drugs (such as lithium, amiodarone, glucocorticoids) can decrease T3 secretion, this phenomenon can represent like hypothyroid, even absence of thyroid disease, term "Non-thyroidal illness". Hence, thyroid function tests should be assessed carefully in the elderly.[56]

With aging change of the pancreas, apoptosis of β-cell occurs. Therefore, insulin production tends to decline with age. On the other hand, aging cell become less sensitive to insulin. The prevalence of insulin resistance is increasing with age, then the pancreas takes action with producing more insulin leading to pancreatic exhaustion. These changes make the elderly hyper-insulinemia and hyperglycemia. So, the prevalence of type 2 diabetes is higher in the elderly.[57,58]

Conclusion

There are aging changes in every organ system, resulting in the risk of developing some diseases such as atherosclerotic diseases, hypertension, diabetes

mellitus, osteoporosis, hypothyroidism or dementia more easily than young adults. It also affects the metabolism of drugs that will be used for treatment. Therefore, it is important to recognize about all these changes for the proper care of the elderly.

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