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Oncogeriatrics (part 2.)
Normal and pathological ageing

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There are two ageing processes, one physiological, also known as normal ageing, and that of pathological ageing, which depends on the occurrence of chronic diseases. The essence of the former is a gradual, progressive, and a very individual restriction of the organs' functional reserve with age. The changes occur in all cells, tissues and systems and do not affect each organ at the same time, and the rate of change can vary between organs. Therefore, the chronological age alone cannot be the factor determining the terapeutic decisions, including surgical treatment. Among the elderly, there is a distinct situation where acute stress response associated with surgery is imposed on the otherwise ageing-related, reduced physiological reserves and the cumulative effect of any accompanying diseases. Standard preparation for surgery and routine perioperative management in such patients can lead to serious complications. In older persons, even minimal injury can exceed the body's capacity to compensate, especially among those with frailty syndrome. It is critical to understand the physiological changes associated with ageing to better understand the differences in the management of these elderly patients.

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Surgery itself is aimed at removing the disease and is most often associated with partial or entire organ excision. In addition, it requires a number of invasive or potentially traumatic activities, such as insertion of cannulas into the vascular system, bladder catheterization, intubation, general anesthesia, etc. All of these lead to local tissue damage, disruption of natural barriers and exposure to external factors (physical, chemical and microbiological). This induces many changes in the body affecting the neuroendocrine, cytokine-immune, water-electrolyte and metabolic systems. This, in turn, may be accompanied by oxidative stress and the associated formation of free radicals [1]. Therefore, in the elderly, we have a particularly critical situation in which the acute stress responses associated with surgery are superimposed on the typical ageing-related decrease in physiological reserves (so-called normal ageing) and the cumulative effect of any accompanying diseases (so-called pathological ageing). Standard preparation for surgery and routine perioperative management in such patients is often insufficient and can lead to serious postoperative complications. In older persons, even relatively minor injuries or trauma can exceed the body's ability to compensate, which is especially the case for those with frailty syndrome. In order to better understand the difference in the management of these patients, it is important to be familiar with the physiological changes associated with the ageing process what will be presented in this part of the series.

The essence of so-called **normal ageing** is a gradual, progressive restriction of the functional reserve, which is the difference between the maximum organ function possible to achieve at a given moment of life and the bare minimum necessary to maintain homeostasis [2]. At present, the ageing process is irreversible and increases over time. However, the rate of decline in any given organ's functional reserve varies between individuals and depends on each individual's genetic

conditions and lifestyle. A reflection of the total depletion of functional reserves and adaptive capacity is the so-called "frailty syndrome". It is characterized by organs and systems becoming "ineffective" in the event of a stress factor (surgery, infection, injury, etc.), resulting in an increased risk of adverse outcomes [3]. The details of the frailty syndrome are thoroughly presented in the first part of the series, in the previous issue of *Nowotwory. Journal of Oncology* [4].

In the case of normal ageing, a number of changes occur in all cells, tissues and systems. These changes do not affect each organ at the same time, and the rate of change can vary between organs.

Aging of the **vascular system** can affect both the heart and the vessels. Changes in the sinus node and other parts of the conduction system lead to the development of cardiac arrhythmias that may clinically manifest themselves through syncope and falls. These changes can also lead to a reduction in the maximum heart rate. In turn, the reduction of vagus nerve tension and the reflex activity of the sympathetic nervous system may lead to an increase in resting heart rate. Within the myocardium, an increase in arterial stiffness results in compensatory left ventricular hypertrophy. Progressive myocardial fibrosis reduces ventricular susceptibility and impairs filling during the contraction phase. Left ventricular contractility is also reduced. Together, this leads to a decrease in the left ventricular ejection fraction and a reduction in exercise tolerance. In addition, vascular changes cause an increase in systolic blood pressure and a decrease in diastolic pressure, which have an adverse effect on coronary blood flow. Reduction of the diastolic capacity of precapillary arterioles has a negative effect on peripheral organ perfusion. Decrease in the sensitivity of the baroreceptors increases the risk of orthostatic hypotension [5–7].

In the **respiratory system**, there are changes in the pulmonary parenchyma, as well as the osteoarticular and muscular system of the chest itself. Consequently, this results in a reduction in vital capacity, a reduction of forced expiratory volume in one second and a worsening of gas exchange in the lungs. The residual volume increases by up to 40%. Due to degenerative changes in the joints, ossification of the cartilaginous joints of the ribs and the decrease in the mass and strength of the respiratory muscles with age, chest mobility decreases and, as a result, so does pulmonary ventilation. The clinical manifestation is the acceleration of the breathing rate at rest and effort dyspnea. Reflex reactions in the upper respiratory tract are weakened, which increases the risk of aspiration of gastrointestinal contents and postoperative pneumonia [8, 9].

Ageing of the **digestive system** is associated with reduced secretion of saliva, gastric juice, bile and pancreatic juice. This leads to a worsening of protein and fat digestion, as well as disorders of iron absorption in the small intestine. The reduction in Castle's intrinsic factor production is the reason for poor absorption of vitamin B_{12} and its overall deficiency. More than 70% of elderly people have lactose intolerance associated with the loss of lactase production by the brush border of the small intestine. Due to changes in diet, low fluid intake, use of diuretics and low physical activity, peristalsis slows and constipation occurs as a result. Liver mass and hepatic blood flow are reduced by 30%. The ability of hepatocytes to regenerate after an injury is likewise reduced. The intensity of metabolic processes is smaller, including those responsible for the metabolism of xenobiotics and drugs [9, 10].

From the fourth decade of life, the number of active nephrons decreases in the **renal system**. Despite compensatory overgrowth of other active nephrons, renal blood flow and glomerular filtration rate are reduced by about 10 ml/min/1.73 m^2/decade and, after 65 years of age, 15 ml/min/1.73 m^2/decade. The decrease in glomerular filtration rate is usually not accompanied by a parallel increase in serum creatinine due to a decrease in creatinine production as a result of decreased muscle mass with age. Due to the reduced elasticity of the bladder walls and weakness of the detrusor muscle, the volume of residual urine increases, which likewise increases the risk of urinary tract infection. Decreased activity of the renin-angiotensin system increases the risk of hyponatremia [11].

Ageing of the **endocrine system** is reflected by the extinction of gonadal hormonal function and a decrease in the secretion of growth hormone, dehydroepiandrostenedione, aldosterone, melatonin, thyroxine and insulin. This leads to osteoporosis and lipid and carbohydrate metabolic disorders, and also promotes hyponatremia. Secondary hyperparathyroidism is a commonly diagnosed disorder among elderly patients. It is most often caused by a vitamin D deficiency, which is associated with skin changes, lower exposure to solar radiation and a nutrient-deficient diet [12, 13].

Changes in the **hematopoietic system** lead to disorders in the normal formation of mature blood cells in the bone marrow. This process becomes more critical after the age 60, when the total number of active bone marrow cells decreases by approximately 50% resulting in approximately 30% of the number of cells observed in youth. Erythropoiesis is the most affected, and further contributes to the development of anaemia in the elderly. The chemotactic, phagocytic and bactericidal activity of neutrophils and macrophages decrease, the proliferation of B and T lymphocytes in response to their stimulation decreases, which leads to an overall decrease in immunity, potentially more severe courses of infection, reduced vaccine effectiveness and an increased risk of cancer [14].

With age, there is also a loss of muscle mass and strength, even in physically active people. Between the ages of 45 and 85, an individual's muscle mass is reduced by about 25%. It is estimated that a significant decrease in muscle mass affects 40% of people over 80 years of age. Muscle strength decreases at an even faster rate; after the age of 60, it is possible to lose up to 3% per year. Local accumulation of triglycerides and lipofuscin within muscle fibers and systemic metabolic

and hormonal disorders (insulin resistance and reduction of growth hormone and IGF-1), as well as ageing-related degenerative changes of motor neurons, contribute to a decrease in muscle mass. The overall effect of muscle changes is not only a decrease in physical fitness, but also an increase in the risk of falls [2,15].

Progressive degenerative changes in the joints lead to a decrease in range of motion, which is often accompanied by pain. In the case of degenerative changes in the intervertebral cervical section, in addition to impaired blood flow in the vertebral arteries (cervico-basal syndrome), there may be neurological symptoms accompanying changes in the lumbar section. The effects of these changes include a change in posture and gait and a decrease in general physical fitness [16,17].

Ageing also leads to significant changes in sensory organs. Hardening of the lens nucleus leads to presbyopia, and a decrease in light transmission through the eye lens leads to deterioration of vision resolution, increased visual impairment in the dark and difficulty distinguishing green-blue shades. A reduction in tear production leads to dry eye and an increased risk of conjunctival infection. Impaired reception of high-frequency tones can cause partial or total deafness. A person's sense of smell may also be impaired due to a loss of nerve endings [18–21].

In the nervous system, the atrophy of hippocampal neurons, reduction of neurotransmitter secretion and receptor density for neurotransmitters lead to reduced cognitive ability, increased risk of depression, prolonged reflex reaction time and a related increase in the risk of falls [22].

The aforementioned changes may be compounded by so-called **pathological ageing**, resulting from the impact of associated diseases on the previously described changes, which are characteristic of normal ageing. The result of this is seemingly disproportionate organ ageing. This process is most often caused by the adverse effects of lifestyle and environmental factors, although it can also be caused, in some cases, by genetic background [2]. Vascular changes including macroangiopathy (atherosclerosis) and microangiopathy (diabetic microangiopathy) are of particular importance in cases like these. Impaired perfusion worsens the function of many organs, including the heart, brain, kidneys, intestines and skeletal muscles. It can also be a common cause of death associated with both heart attacks and strokes. Smoking, dust exposure and recurrent lower respiratory tract infections can lead to a faster reduction in lung function and pulmonary reserve. Obesity accelerates the course of degenerative joint processes and reduces the functional reserve of the heart and lungs, in addition to having adverse effects on metabolic

Table I. Review of the organ changes associated with normal aging [2–25]

Vascular system	Reduction in the maximum HR, increase in resting HR, compensatory left ventricular hypertrophy, reduced ventricular ejection fraction, increase in systolic blood pressure, decrease in diastolic pressure, reduction in the coronary blood flow and organ perfusion, decreased sensitivity of the baroreceptors. **Clinical manifestation**: arrhythmias (leading to syncope and falls), reduced exercise tolerance, orthostatic hypotension.
Respiratory system	Reduction in VC, reduction in FEV_1, worsening of gas exchange in the lungs, increased RV, reduced pulmonary ventilation, weakened reflex reactions in the upper respiratory tract. **Clinical manifestation**: acceleration of the breathing rate at rest and effort dyspnoea, increased risk of aspiration and postoperative pneumonia.
Digestive system	Reduced secretion of saliva, gastric juice, bile and pancreatic juice, reduced peristalsis, reduced liver mass and hepatic blood flow, reduced regeneration of the hepatocytes after injury. **Clinical manifestation**: worsened digestion of protein and fat, constipations, vitamin B_{12} deficiency, reduced metabolism of xenobiotics and drugs.
Renal system	Reduction in the number of active nephrons decreases, decreased renal blood flow and glomerular filtration rate, reduced elasticity of the bladder walls and weakness of the detrusor muscle. **Clinical manifestation**: increase in the volume of residual urine increases the risk of infection.
Endocrine system	Decrease in the secretion of growth hormone, dehydroepiandrostenedione, aldosterone, melatonin, thyroxine and insulin, vitamin D deficiency. **Clinical manifestation**: osteoporosis, lipid and carbohydrate metabolic disorders, increased risk of hyponatremia.
Hematopoietic system	Decrease in active bone marrow cells (particularly erythropoiesis), decrease of the chemotactic, phagocytic and bactericidal activity of neutrophils and macrophages, decrease in the proliferation of B and T lymphocytes in response to their stimulation. **Clinical manifestation**: anaemia, overall decrease in immunity, potentially more severe courses of infection, reduced vaccine effectiveness, increased risk of cancer.
Musculoskeletal changes	Increased adiposity, reduced muscle mass, reduced grip strength, reduced body weight. **Clinical manifestation**: decrease in physical fitness, increase in the risk of falls.
CNS and sensory organs	Atrophy of hippocampal neurons, reduction of neurotransmitter secretion and receptor density for neurotransmitters. **Clinical manifestation**: reduced cognitive ability, increased risk of depression, prolonged reflex reaction time, increase in the risk of falls. Presbyopia, deterioration of vision resolution, difficulty in distinguishing green-blue shades, increased risk of conjunctival infection, partial or total deafness, deterioration of the smell.

HR – hearth rate, VC– vital capacity, FEV_1 – forced expiratory volume in one second, RV – residual volume

processes, including those associated with an increase in the risk of type 2 diabetes. Exposure to loud noises accelerates the ageing and degradation of the hearing organ. Exposure to ultraviolet radiation accelerates skin ageing. Exposure to ionizing and infrared radiation accelerates the development of cataracts. Hard physical work and injuries likewise accelerate the degeneration of joints [23, 24].

The effect of postoperative stress is more detrimental to some organs than others. Therefore, the leading causes of postoperative mortality among the elderly are: myocardial infraction, pulmonary and cerebrovascular complications [2, 25]. Therefore, preoperative comprehensive geriatric assessment of organ function and reserves should be obligatory in the older population, particularly undergoing cancer surgery.

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