Physiology of Aging

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4.1 Introduction

Our population is aging at an astonishing rate. According to the US census, the US population totaled about 321 million in 2015, and 14.9% were over the age of 65. By the year 2050, this percentage is expected to grow to 22.1% [1]. The explosive growth of the older population is attributable to the aging of the baby boomers, increasing longevity, and declining fertility rates. In 2008, older adults accounted for 26% of physician office visits and 35% of hospital stays. That same year, the geriatrician physician workforce only numbered about 7100 [2]. We are staggeringly underprepared to care for our aging population.

You will likely care for older adults in whatever specialty you choose to practice and will need to be able to distinguish between the changes expected with normal aging and changes that indicate underlying pathology. The difference between normal and pathological aging is often a subtle one. In his piece titled "The Way We Age Now," Atul Gawande reflected on the changes of normal aging:

> » Even as our bones and teeth soften, the rest of our body hardens. Blood vessels, joints, the muscle and valves of the heart, and even the lungs pick up substantial deposits of calcium and turn stiff… As we age, it's as if the calcium flows out of our skeletons and into our tissues [3].

The aging body experiences a number of changes that may increase vulnerability to disease. Individuals, and even different organ systems within the same person, age at varying rates depending on various lifestyle and environmental factors [4].

A key concept in understanding aging is homeostenosis, which refers to the reduced physiologic reserve available to respond to stress in older adults. Due to the changes of aging, the older adult uses more physiologic resources simply to maintain homeostasis. With depleted reserves, the older adult may experience a greater frequency and severity of illness [4]. This chapter reviews the expected physiology of aging by organ system.

4.2 Aging of the Cardiovascular System

This section will discuss the effects of aging on the structure and physiology of the vasculature, including the arteries and veins, and the heart.

4.2.1 Arteries

Reviewing the anatomy of the arteries is helpful in understanding the changes of the aging arterial system. Arteries consist of three layers, aptly called tunics, from the outermost to the innermost layer:

1. Tunica adventitia (outermost layer)—Composed of proteins, collagen, and elastin. Adventitia simply means an "additional" layer.
2. Tunica media (middle layer)—Consists largely of smooth muscle cells that propel blood through the arteries.
3. Tunica intima (innermost layer)—Contains the endothelium, a protective and dynamic inner layer that helps regulate arterial dilation and constriction, angiogenesis (creation of new arteries), thrombosis (clotting), and thrombolysis (clot-busting) [5].

The makeup of arterial walls changes over time. They continually stretch and recoil to circulate blood, causing elastin to fray and wear out much like a used rubber band. Collagen takes the place of elastin in the tunica intima (inner layer), and the number of smooth muscle cells in the tunica media (middle layer) becomes fewer. The loss of elastin and smooth muscle cells causes the arterial wall to become less elastic and pliant [5]. With the loss of elasticity, large arteries become stretched out over time, much like your favorite winter sweater, and increase in diameter and length [6] (Fig. 4.1). Additionally, even in the absence of atherosclerosis, the thickness of the intimal and medial arterial layers triples between 20 and 90 years of age [7]. Age-related thickening of the arterial wall is a risk factor for atherosclerosis. Lastly, healthy endothelial cells release nitric oxide to help arteries relax. Over time, endothelial cells malfunction and produce less nitric oxide, further stiffening the arteries.

All of these age-related structural changes harden and stiffen the large arteries, leading to increased systolic and decreased diastolic blood pressures and predisposing older people to atherosclerosis, particularly in developed countries. Hypertension and atherosclerosis increase the risk of heart disease, myocardial infarction, stroke, and renal disease. Common risk factors of diabetes, high cholesterol, smoking, obesity, and physical inactivity compound the effects of aging on the vascular system.

4.2.2 Veins

Like arteries, veins stretch over time and become less elastic. One-way valves in healthy veins prevent backward blood flow. However, as these valves weaken with age, blood pools and engorges the veins, causing varicose veins. Venous insufficiency, combined with the downward pull of gravity, causes edema in the legs.

4.2.3 Cardiac Changes

4.2.3.1 Left Ventricular Hypertrophy

As noted earlier, the stiffening of large arteries contributes to hypertension. Hypertension increases cardiac afterload. The heart has to work harder during systole (period in the cardiac

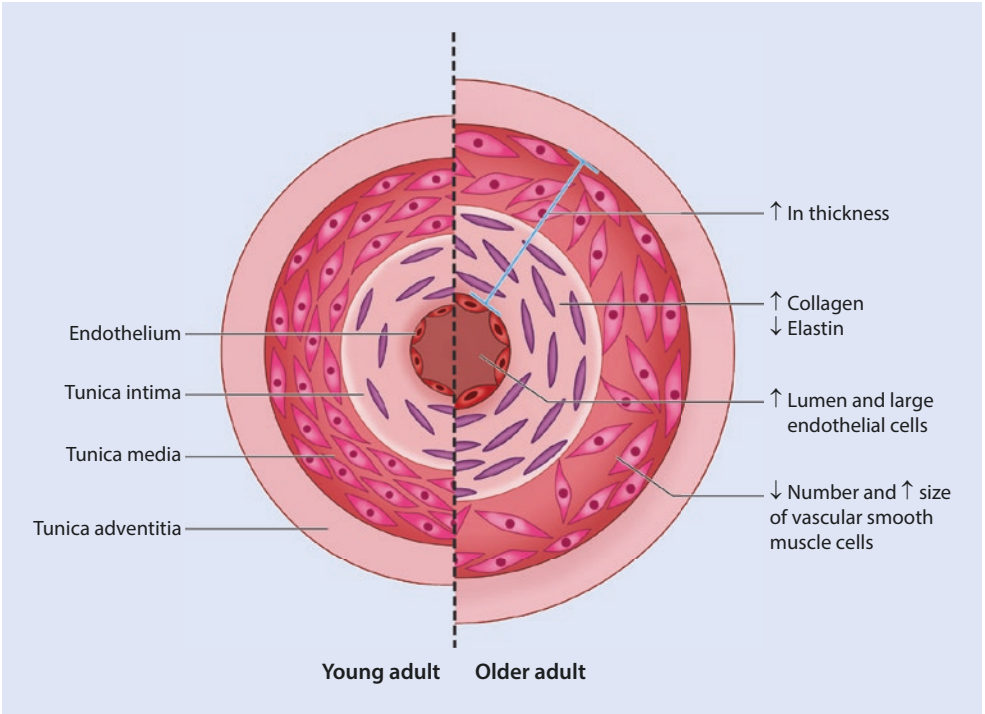

Fig. 4.1 Shows remodeling of central arteries with age. There are significant changes in each of the layers of the arterial wall. The intimal and medial layers thicken. In the intimal layer, collagen replaces elastin. The number of smooth muscle cells in the medial layer decreases. (Modified from: Fillit et al. [29])

cycle when the ventricles contract) to push blood through stiff arteries. Working harder causes the heart muscle to enlarge and stiffen, resulting in left ventricular hypertrophy (Fig. 4.2a, b). As the left ventricular walls hypertrophy, they do not gain healthy muscle, but instead fibrose, calcify, and acquire fatty deposits. S4, also known as an atrial gallop, is actually a normal finding on the physical exam of an older patient. It represents blood forced from the left atrium slapping against the stiffened walls of the left ventricle.

Now, let's talk about what happens in diastole with aging and the development of left ventricular hypertrophy. During diastole, the left ventricle relaxes and fills with blood. Due to hypertrophy, the left ventricular cavity stiffens and shrinks in size. It is no longer able to relax or stretch to accommodate blood from the left atrium. Blood then backs up in the left atrium and overspills into the lungs, causing pulmonary edema and shortness of breath. In short, heart failure results. Depending on the severity of heart failure, the right side of the heart may also fail. Because of left ventricular diastolic dysfunction, older adults are prone to more frequent and severe heart failure exacerbations.

4.2.3.2 Decreased Heart Rate and Cardiac Output in Response to Stress

The maximal heart rate achieved in response to exercise or stress also decreases with age, partly because the heart becomes less sensitive to the beta-adrenergic stimulation of the sympathetic nervous system (which regulates the body's "fight-or-flight" response). In fact, the target maximal heart rate is calculated as "220-age" [8]. We learn in physiology that cardiac output, the blood volume pumped out by the left ventricle each minute, is the product of stroke volume and heart rate (CO = SV × HR). Due to decreased heart rate, the older heart is less able to increase cardiac output in response to physiologic stress [9].

4.2.3.3 Orthostatic Hypotension

When someone stands, gravity causes blood to pool in the legs, resulting in decreased blood supply to the heart and brain. Usually, baroreceptors (sensors that detect changes in blood pressure) respond to drops in blood pressure by constricting arteries and increasing heart rate in order to maintain blood pressure. Many older adults, however, have a blunted baroreceptor response such that the body is not able to adapt to decreases in blood pressure.

Orthostatic hypotension (an abnormal decrease in blood pressure that occurs with standing) becomes more common among older adults due to decreases in baroreceptor sensitivity, arterial and cardiac compliance, plasma volume, and vasopressin (also known as antidiuretic hormone) response. This decreases cerebral perfusion, resulting in syncope (transient loss of consciousness) and falling [6].

4.2.3.4 Valvular Disease

The aortic and mitral valves thicken and calcify over time, increasing prevalence of valvular diseases, such as aortic and mitral regurgitation and stenosis.

4.2.3.5 Atrial Fibrillation

The left atrium stretches to accommodate the backup of blood from a failing and hypertrophied left ventricle or malfunctioning mitral valve (Fig. 4.2a, b). The stretching of the left atrial walls may disrupt the heart's electrical circuits, increasing the risk of atrial fibrillation.

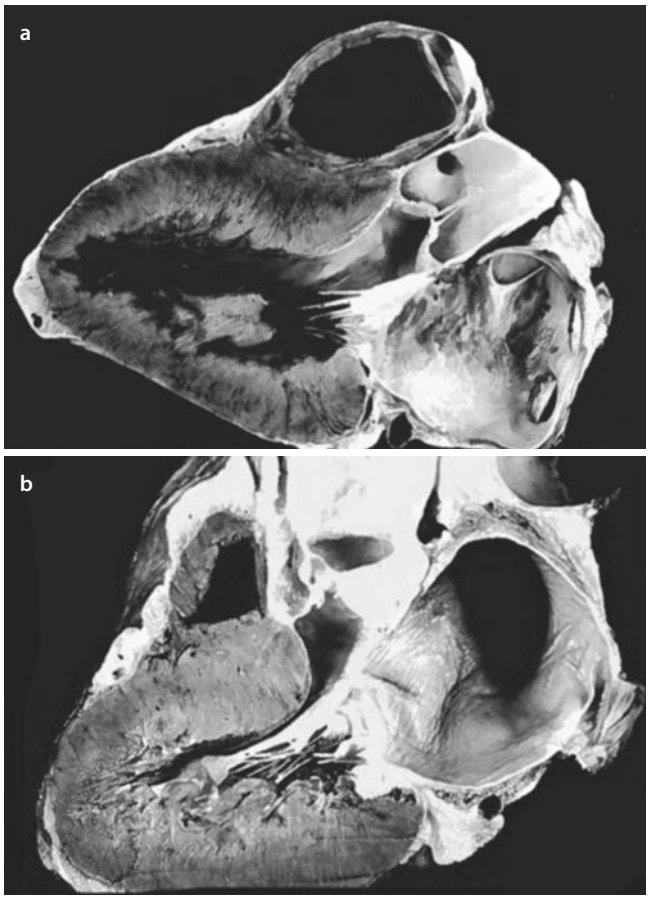

Fig. 4.2 **a** Normal heart from an 18-year-old for comparison (left ventricular long axis view). **b** Normal heart from an 84-year-old man shows decreased size of left ventricular cavity, dilated aortic root, and left atrial dilatation. (Reprinted with permission from: Halter et al. [30])

4.2.3.6 Sick Sinus Syndrome

By age 75, only 10% of pacemaker cells in the sinus node (the heart's primary pacemaker) remain [9]. Due to the loss of pacemaker cells, older adults are more prone to sick sinus syndrome. This syndrome causes abnormal heart rates and is also known as tachycardia-bradycardia syndrome (Table 4.1).

4.3 Aging of the Pulmonary System

Ever wonder why older adults become so ill when they get pneumonia and may even need to be admitted to the hospital?

The respiratory changes caused by aging may not be clinically significant in the healthy older adult. However, as the lungs age, they are less able to compensate for respiratory stresses, such as pneumonia. This section will describe the impact of aging on three components of respiration [10]:

1. Lung parenchyma
2. Chest wall compliance
3. Respiratory muscles

Table 4.1 Aging of the cardiovascular system

Changes in structure	
Age-associated changes	*Possible consequences*
↑ Vascular intimal thickening	Atherosclerosis
↑ Vascular stiffness	Systolic hypertension Atherosclerosis
↑ Left ventricular wall thickness → ↓ Cardiac diastolic filling	Pulmonary edema Heart failure
↑ Left atrial size → disrupts electrical circuits	Atrial fibrillation
Changes in function	
Age-associated changes	*Possible consequences*
Altered regulation of vascular tone Vascular stiffening	Hypertension
↓ Cardiovascular reserve	↑ Frequent heart failure exacerbation ↑ Severity of heart failure

4.3.1 Changes in Structure and Function of the Pulmonary System

1. Lung Parenchyma

Over time, lung mass decreases because the number of alveoli (small sacs responsible for gas exchange between the lungs and bloodstream) dwindles. The lungs lose elasticity and are less able to expand and recoil. When the lungs are not able to fully open, intrathoracic negative pressure drops, causing airway collapse and decrease in alveolar surface area by as much as 20% [7, 11]. This collapse is known as atelectasis, which then leads to a ventilation-perfusion (V/Q) mismatch. In this case, a V/Q mismatch means that inadequate air is available in the alveoli for gas exchange with the blood, causing lower blood oxygen levels.

Due to the loss of elastic recoil, the lungs also hyperinflate over time, mimicking the disease process of chronic obstructive pulmonary disease (COPD) [10, 12]. In fact, this process of aging is also known as "senile emphysema."

Pulmonary function test parameters change with aging. Forced expiratory volume (FEV), the total volume of air exhaled after maximum inspiration, and forced expiratory volume in 1 second (FEV1), the volume of air exhaled after maximum inspiration in 1 second, both decrease. Consequently, the residual volume (amount of remaining air in the lungs after maximal expiration) increases about 10% per decade [4]. Due to hyperinflation of the lungs, older people have smaller tidal volumes and consequently may have a higher respiratory rate [11]. As a result of these changes in pulmonary function parameters, functional reserve decreases, and older people are less able to compensate for physiologic stress.

Diffusion capacity of carbon monoxide (DLCO), a measure of the efficiency of gas exchange, becomes less effective due to both structural changes and V/Q mismatch, as previously described [11].

2. Chest Wall Compliance

Chest wall compliance decreases with age due to both stiffening of the chest wall and altered shape of the thoracic cavity. The chest wall becomes less compliant as rib cartilage ossifies. The spine shortens due to the loss of intervertebral space and the compression of vertebral bodies, shrinking and stiffening the thoracic cage. Osteoporosis may cause vertebral collapse [11]. These skeletal changes result in kyphosis, or a rounded upper back, and a barrel-shaped chest, limiting the capacity of the lungs to expand and recoil.

3. Respiratory Muscles

Respiratory muscles, including intercostal muscles and the diaphragm, weaken over time. Due to the shrinking of the thoracic cage, the diaphragm flattens and generates less force. Because of the increased effort needed to breathe, the older person may expend 120% more energy than a young adult needs to breathe [11].

4.3.1.1 Increased Susceptibility to Pneumonia

Older adults may be less able to perceive respiratory symptoms due to reduced sensation, impaired cognition, or even deconditioning, leading to more subtle and delayed presentations of respiratory problems.

They may lose the strength needed to generate an effective cough, or may develop impaired swallowing ability (dysphagia) in the setting of stroke or neurological disease. A weaker cough or dysphagia increases the risk of aspiration pneumonia.

Glandular epithelial cells decrease in number and produce less mucous, which traps bacteria. Cilia (hair-like structures in the respiratory tract) are less able to clear the respiratory tract effectively. The combination of a weaker cough, less mucous, and less effective ciliary action means that older people are less able to defend against respiratory infections [11] (Table 4.2).

Table 4.2 Aging of the pulmonary system

Changes in structure	
Age-associated changes	*Possible consequences*
Chest wall stiffening and ↓ elasticity of parenchymal fibers ↓ elastic recoil of the lungs → lung hyperinflation ↓ Alveoli → ↓ lung mass	↓ Pulmonary reserve
↓ Effectiveness of ciliary action → ↓ Ability to clear secretions	↑ Respiratory infections
Respiratory muscles (including diaphragm) weaken	↓ Effectiveness of cough ↑ Shortness of breath ↑ Atelectasis

4.4 Aging of the Gastrointestinal System

This section will describe the age-associated changes of the gastrointestinal system by considering the gastrointestinal tract from the mouth to the colon and then concluding with a brief description of age-related changes in the liver, pancreas, and gallbladder.

4.4.1 Mouth

As we age, saliva glands in the mouth atrophy and produce less saliva. Due to the decreased production of saliva and the prevalent use of medications that cause xerostomia (dry mouth) as a side effect, up to 40% of healthy older adults experience xerostomia [13]. Dryness renders the mouth more vulnerable to cavities, oral infections, and gum disease [14].

The gums recede, causing teeth to loosen and fall out and increasing the risk of malnutrition. Jaw muscles weaken such that older adults are less able to chew foods of a hard or tough consistency. Further, the combination of dry mouth, poorly fitted dentures, and weakened chewing power may contribute to dysphagia (swallowing difficulties) in older adults [15].

4.4.2 Esophagus

With age, food moves more slowly from the mouth to the esophagus. The slowed movement of food occurs both because the oropharyngeal muscles slow and the upper esophageal sphincter takes longer to relax. The prolonged transit time of food increases the risk for silent aspiration. However, these changes usually only become clinically significant in the presence of pathology, such as dementia, neurodegenerative disease, or neck radiation or surgery [15].

In the aging esophagus, peristaltic contractions may become weaker. In addition, the esophagus dilates in size. The lower esophageal sphincter weakens and is also less able to fully relax [15]. When the lower esophageal sphincter does not fully open, the esophagus is less able to clear gastric acid, leading to gastroesophageal reflux disease (GERD) and damage to the esophageal mucosa. Because of decreased acid clearance, GERD symptoms may last longer in older adults [13]. GERD-related damage to the esophageal mucosa may cause a benign esophageal stricture.

The weakness of the lower esophageal sphincter may allow a part of the stomach to protrude through the hiatus (opening) in the diaphragm, exacerbating GERD. Up to 60% of people over age 60 have hiatal hernias [13].

Odynophagia (painful swallowing) in older adults may arise due to GERD, chemotherapy, radiation, and medications, such as NSAIDs, aspirin, and alendronate.

4.4.3 Stomach

- *Delayed gastric emptying*: The stomach empties more slowly, meaning that older people may experience satiety more quickly and have longer periods of abdominal distention. Delayed gastric emptying may both decrease appetite and increase exposure to toxic medications, such as NSAIDs.
- *Decreased production of prostaglandin*: The production of prostaglandin (a substance responsible for lowering acid levels in the stomach) decreases with age, meaning that older people may be more susceptible to gastritis or to gastric irritants, such as NSAIDs. NSAIDs further lower prostaglandin levels by blocking the cyclooxygenase assembly pathway that produces prostaglandin [4].
- *Helicobacter pylori*: *Helicobacter pylori* infection in the stomach and duodenum becomes more common with age [4]. In fact, more than 50% of older people have *H. pylori* infection. The reason for increased *H. pylori* prevalence among older people is unknown. *H. pylori* is associated with gastric ulcers, pernicious anemia (anemia that results from the inability of gastric parietal cells to produce intrinsic factor, preventing the absorption of vitamin B12 and leading to the underproduction of red blood cells), and gastric lymphoma [15]. Gastric ulcers in older adults are more likely to bleed and may take longer to heal.
- *Stress ulcers*: The stress of hospitalization in older adults results in a higher production of cortisol (stress hormone), which, in turn, heightens the risk for stomach ulcers. Proton pump inhibitors (PPIs) are routinely given to older hospitalized patients to decrease gastric acid production and protect against stomach ulcers. PPIs are most effective for short-term treatment of uncomplicated GERD (up to 8 weeks) and should be discontinued after hospitalization [16].

4.4.4 Small Intestine

- *Decreased calcium absorption*: The small intestine absorbs less calcium with age due to lower levels of vitamin D in the blood and fewer vitamin D receptors in the small intestine [4]. Reduced calcium absorption contributes to bone loss in the older adult.
- *Bacterial overgrowth*: Bacterial overgrowth in the small intestine is more common in older adults. It is unclear if small bowel bacterial overgrowth is attributable to medications that slow bowel transit time, immobility, comorbidities such as diabetes, or advancing age [13]. Bacterial overgrowth further exacerbates the malabsorption of nutrients [4].

4.4.5 Colon

- *Slowed colonic transit*: The effect of aging on motility of the colon is unknown. It appears that colonic peristaltic contractions may weaken with age. The time required for fecal matter to pass through the colon may increase over time. However, it is thought that prolonged colonic transit time may be due to medications, comorbidities, and immobility, rather than aging [13].
- *Diverticulosis*: Parts of the colonic wall weaken over time due to increased intraluminal pressure caused by constipation and consequent straining during bowel movements as well as decreased muscle strength. The weak spots in the colonic wall form pouches known collectively as diverticulosis. More than 65% of those over age 65 have diverticulosis [4]. Diverticulitis occurs when one or more of these pouches become inflamed (Fig. 4.3).

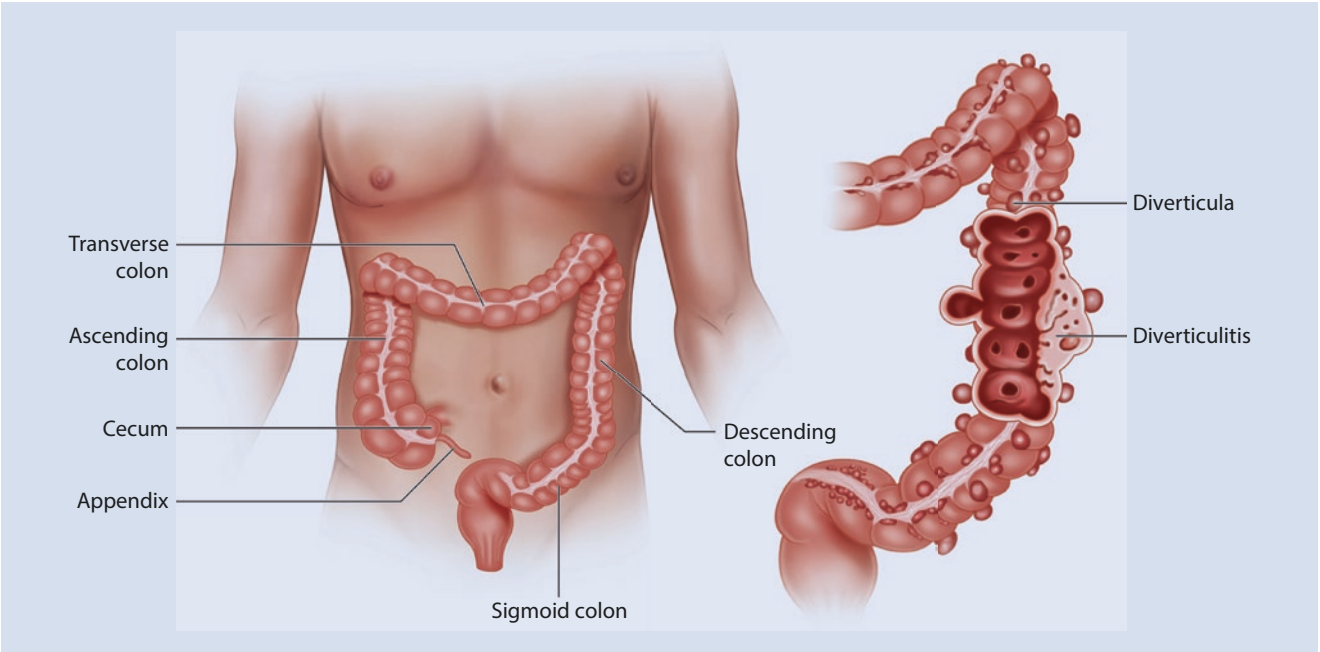

Fig. 4.3 Diverticulosis and diverticulitis. (Modified from: Mayo Clinic [31])

- *Constipation*: Constipation becomes more common among older adults. Over time, colonic contractions weaken and rectal sensation diminishes. Older adults are more likely to have risk factors for constipation, such as immobility, low-fiber diet, and use of constipating medications.
- *Hernias and hemorrhoids*: Older adults experience greater prevalence of hernias due to the weakening of the abdominal wall over time. Hemorrhoids (engorged veins in the anus or rectum) also become more common due to increased pressure in the rectum caused by constipation.
- *Intestinal ischemia*: Blood flow to the splanchnic vessels decreases over time partly due to atherosclerosis and may lead to chronic intestinal ischemia.
- *Decreased anorectal sphincter tone*: The resting anorectal sphincter tone decreases in both older men and women. It has been observed that older women are more prone to fecal incontinence due to pelvic floor dysfunction and decreased maximal anorectal sphincter tone, rectal compliance, and sensation [13].

Table 4.3 Aging of the gastrointestinal system

Changes in structure	
Age-associated changes	*Possible consequences*
↓ Saliva production	↑ Oral infections ↑ Gum disease
↓ Liver size and blood flow	Impaired drug clearance (i.e., acetaminophen)
↓ Pancreatic mass	Insulin resistance
Changes in function	
Age-associated changes	*Possible consequences*
↓ Prostaglandin	Gastritis
↑ *Helicobacter pylori*	Gastric ulcers Pernicious anemia Gastric lymphoma
Impaired acid clearance	Gastroesophageal reflux disease (GERD)
Slowed gastric emptying	Prolonged gastric distention ↑ Postprandial satiety
↓ Calcium absorption	↑ Bone loss
↓ Rectal wall sensitivity Weaker colonic contractions	Constipation
↓ Strength in smooth muscles of colon wall	↑ Diverticulosis
↓ Insulin secretion	↑ Insulin resistance

4.4.6 Liver

With age, liver size and hepatic blood supply decrease. Older adults are more sensitive to the side effects of medications and toxins in part because the liver is less able to quickly metabolize them [13].

4.4.7 Pancreas

The pancreas shrinks over time and produces less insulin, thereby leading to insulin resistance and increasing the risk of diabetes.

4.4.8 Gallbladder

Older adults tend to have larger bile duct diameters than younger adults do. They are more prone to gallstones because the biliary secretion of cholesterol increases while the secretion of bile acids decreases. A higher level of cholesterol in bile means more gallstones [15] (Table 4.3).

4.5 Aging of the Urinary System

4.5.1 Upper Urinary Tract: Kidneys and Ureters

Kidneys become smaller with age. Because 30% of glomeruli (network of capillaries in the nephron that filters blood) sclerose by age 75, the kidneys become less selective filters [4]. To compensate, the remaining glomeruli are forced to filter a greater volume of blood. This compensatory mechanism is known as hyperfiltration. The increased blood flow creates shear stress that damages the glomeruli, causing further sclerosis. As the number of functioning glomeruli decreases, the glomerular filtration rate (GFR), the rate at which the kidneys filter blood, falls [17]. Due to their compromised filtering capacity, the kidneys are less able to excrete medications and toxins. Therefore, it is crucial to consider renal compromise when dosing medications for older adults.

Creatinine becomes a less reliable marker of kidney function in older adults. Muscle produces small amounts of creatinine. As muscle mass decreases in older adults, creatinine levels fall and do not accurately reflect kidney function. The Modification of Renal Diet (MDRD) study equation is commonly used to accurately calculate GFR in older patients.

Like the rest of the arterial system, renal arteries become less elastic and stiffen over time. They constrict rather than dilate and often develop atherosclerosis, reducing blood flow to the kidneys. Renal blood flow may decrease from about 600 mL/min in a young adult to 300 mL/min in an older adult [18]. For this reason, older people are more susceptible to kidney injury during acute illness, such as sepsis, heart failure, or dehydration, that results in a decreased circulating plasma volume.

Renal tubules decrease in number and length and lose the ability to concentrate urine over time, such that fluid and electrolyte abnormalities are more common, particularly with physiologic stress.

Dehydration and hypernatremia are common among older adults because they may have decreased sensation of thirst and less urge to drink water. For example, people who have dementia are less likely to feel thirsty and those who are immobile do not have access to water [19].

Further contributing to the risk of dehydration, older kidneys are less responsive to water or salt depletion [19]. The renin-angiotensin-aldosterone (RAA) system regulates the body's sodium and fluid balance and blood pressure. Renin, angiotensin, and aldosterone levels decrease over time, meaning that the older adult is more at risk for volume depletion and hyperkalemia.

At the same time, antidiuretic hormone (ADH) baroreceptors (pressure sensors) become less sensitive to decreased circulating plasma volumes and fail to release enough ADH. In turn, the kidneys become less sensitive to ADH and are thus less able to retain sodium and water in response to volume depletion.

Hyponatremia is more common among older adults. As the GFR declines, the proximal tubule has more time to reabsorb free water. Less free water reaches the distal tubules, meaning that the kidneys are less able to dilute urine or excrete free water. Hyponatremia results. Although usually mild and asymptomatic in older people, hyponatremia is associated with higher mortality, falls, fractures, cognitive impairment, hospitalization, and nursing home placement [19].

Older kidneys also activate less vitamin D, contributing to vitamin D deficiency (Table 4.4).

Table 4.4 Aging of the upper urinary tract

Changes in structure	
Age-associated changes	*Possible consequences*
↓ Kidney size, mass, and number of functional glomeruli	↓ Renal function
↓ Number/length of functional renal tubules	↑ Fluid and electrolyte abnormalities
↓ Renal blood vessel elasticity	↓ Renal blood flow
Changes in function	
Age-associated changes	*Possible consequences*
↓ Creatinine clearance and glomerular filtration rate (GFR)	↓ Excretion of drugs and toxins
↓ Concentrating/diluting capacity	↑ Fluid and electrolyte abnormalities
↓ Serum renin and aldosterone	Volume depletion ↑ Risk of hyperkalemia
↓ Vitamin D activation	Vitamin D deficiency

4.5.2 Lower Urinary Tract: Bladder and Outlet

The lower urinary tract consists of the bladder and urethra. It stores and voids urine and also protects the kidneys from external infectious agents [18]. A healthy adult usually has voluntary control over urination. However, the aging of the nervous system and the lower urinary tract results in decreased voluntary control of voiding (Fig. 4.4).

It is important to understand lower urinary tract symptoms as manifestations of a syndrome [18]. The process of urination is complex and requires the coordination of multiple systems. Let's review the components of successful urination in a healthy adult. The detrusor muscle (muscular wall of the bladder) generates the force needed to empty the bladder. The parasympathetic nervous system stimulates urination. Pelvic nerves release acetylcholine, which stimulates the muscarinic receptors in the bladder and signals the detrusor muscle to contract and void [18]. At the same time, the urethral sphincter relaxes in order to allow urine to pass. The older adult also needs to have intact cognition and mobility to be able to respond to the urge to urinate.

Any number of these components may fail in the older adult, resulting in lower urinary tract symptoms. The number of muscarinic receptors decreases with age, such that the detrusor muscle does not receive the signal to contract [18]. In the presence of cognitive impairment and degenerative disease, older brains have decreased sensitivity to bladder volume and ability to coordinate urination. Due to limited mobility, some older people may not reach the toilet in time and may experience urinary incontinence.

Urinary symptoms fall into the following three categories:

1. *Irritability*: The hallmarks of an overactive, or irritable, bladder include nocturia and increased urge and frequency. An older adult with an overactive bladder makes more trips to the bathroom during the night, increasing the risk of falls.
2. *Retention*: Symptoms of hesitancy, incomplete emptying, and pelvic discomfort indicate an underactive bladder.
3. *Incontinence*: Older people are more likely to experience urinary incontinence due to decreased detrusor muscle strength, bladder elasticity and capacity, sensitivity to bladder volume, and ability to control the timing of voiding. For instance, if an older person experiences a delay in sensing bladder fullness due to impaired cognition or sensory nerves, he or she may have less time between the initial urge to urinate and the leakage of urine, resulting in an episode of incontinence. Urinary incontinence alone may lead to caregiver strain and increase the risk of nursing home placement [18].

Women and men have different risk factors for developing lower urinary tract symptoms. In women, lower estrogen lev-

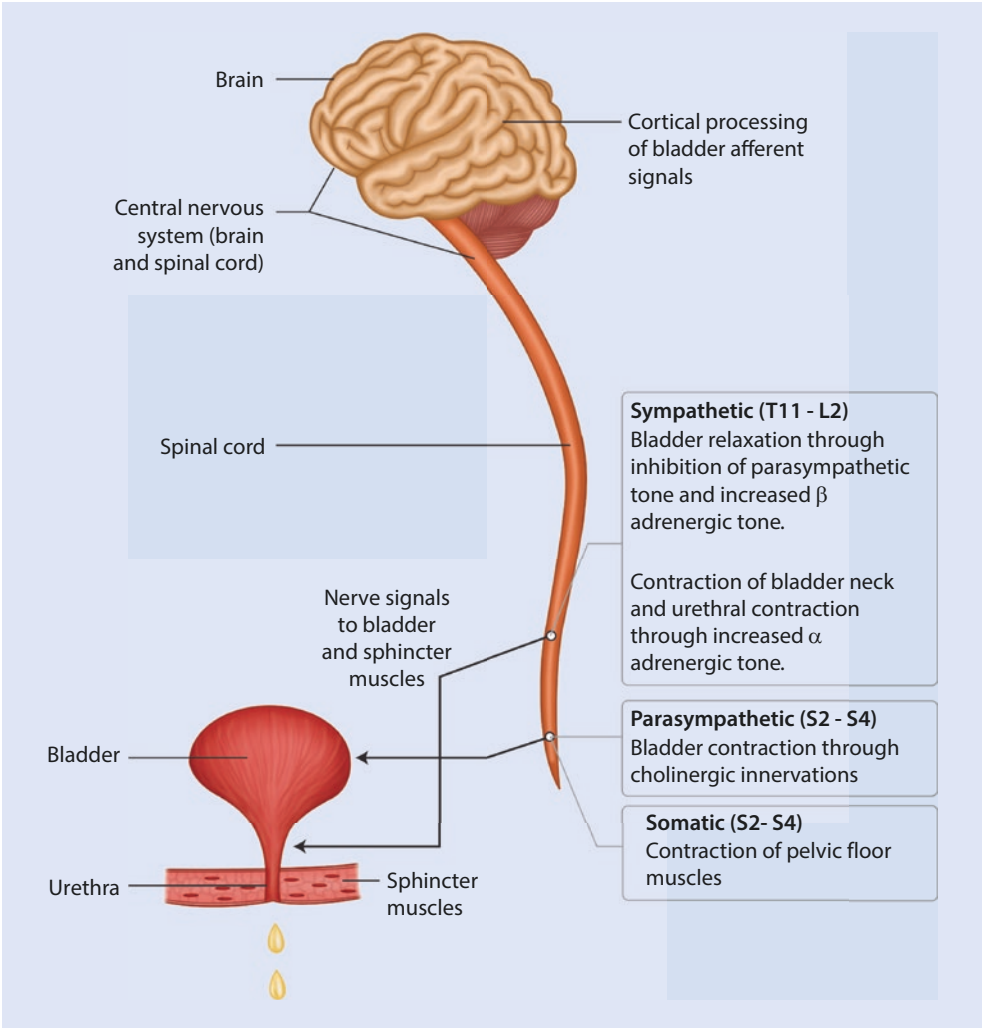

Fig. 4.4 Shows involvement of central and peripheral nervous system in urination. (Reprinted with permission from: Halter et al. [30])

els lead to urethral shortening, increasing exposure to bacteria. Pelvic organ prolapse is also common due to the weakening of pelvic floor muscles, particularly if a woman has a history of multiple vaginal births. Vaginal prolapse in women may cause irritative or obstructive symptoms. In men, benign prostatic hypertrophy (BPH) may cause urinary hesitancy and retention and nocturia.

Other disease processes may exacerbate urinary incontinence. Fecal impaction can increase pressure on the bladder, causing incontinence. Obesity, dementia, and diabetic neuropathy also increase risk of urinary incontinence (Table 4.5).

Table 4.5 Aging of the lower urinary tract

Changes in structure	
Age-associated changes	*Possible consequences*
↓ Detrusor muscle strength ↓ Bladder capacity ↓ Bladder elasticity	↑ Urinary incontinence
Changes in function	
Age-associated changes	*Possible consequences*
↑ Cognitive impairment ↑ Neurodegenerative disease ↓ Mobility	↓ Voluntary control of urination ↑ Urinary incontinence

4.6 Aging of the Endocrine System

The levels of most hormones decrease with age, starting at around 30 years of age, and continue to decline at about 1% per year [20] (Fig. 4.5). The body secretes most hormones in a circadian rhythm, which becomes more irregular with age [20]. Older people are also more likely to have autoimmune diseases that result in decreased hormone levels.

4.6.1 Pineal Gland

The pineal gland is a small endocrine organ beneath the thalamus that makes melatonin. The name of the gland arises from the Latin word for "pine cone" and refers to the gland's shape. The diurnal rhythm of melatonin secretion changes with time and may cause disruptions in sleep-wake

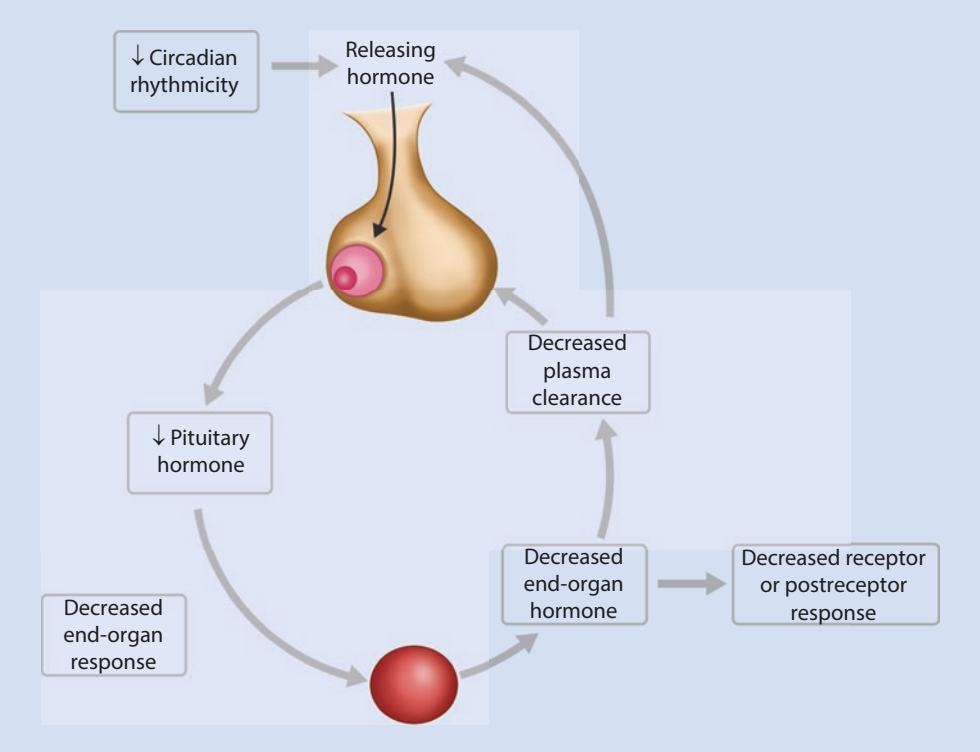

Fig. 4.5 Shows hormonal changes of aging. Hormone levels generally decline with aging. Circadian rhythm also declines. The response of receptors and post-receptors is less robust. (Reprinted with permission from: Fillit et al. [29])

cycles, such as insomnia. Reduced exposure to bright daylight in the older population may decrease secretion of melatonin [21].

4.6.2 Thyroid

The older thyroid may develop nodules and fibrosis, requiring thyroid hormone replacement therapy such as levothyroxine. Older people are also more prone to acquire both clinical and subclinical hypothyroidism and hyperthyroidism. The presentations of these syndromes are both atypical and have similar characteristics in the older population. Symptoms of fatigue, constipation, cognitive impairment, depression, and weight loss are not only more common among older people but are also symptoms of both hypothyroidism and hyperthyroidism, rendering diagnosis challenging [20, 21]. What is known as "apathetic hyperthyroidism," for instance, may present with depression in the older adult [21].

4.6.3 Female Gonads

A woman is born with a limited number of oocytes, which deplete over time until menopause. Menopause begins after 1 year of amenorrhea. On average, women undergo menopause at about 52 years of age [22].

Follicle-stimulating hormone (FSH), produced in the pituitary, stimulates a dwindling number of oocytes to produce estrogen, resulting in declining estrogen levels. In response to lower estrogen levels, FSH level increases prior to and during menopause and is a hallmark laboratory finding of menopause. Decreased production of estrogen causes common menopausal symptoms, including hot flashes, vaginal dryness and dyspareunia, and increasing fracture risk.

4.6.4 Male Gonads

Dehydroepiandrosterone (DHEA) and its sulfated form (DHEA-S), the precursors of female and male sex hormones such as estradiol, progesterone, and testosterone, decrease with age. Production of androgens over time decreases in part due to declining adrenal output.

Testosterone levels decrease with age due a decline in the functioning of the hypothalamic-pituitary axis. The hypothalamus secretes less gonadotropin-releasing hormone (GnRH), consequently decreasing the amount of luteinizing hormone (LH) produced by the pituitary gland. LH stimulates Leydig cells in the testes to produce testosterone. Less LH stimulation of declining Leydig cells means less testosterone production. Once testosterone is released into the bloodstream, it binds to sex hormone-binding globulin (SHBG). With age, SHBG increases such that less free testosterone is available.

The number of seminiferous tubules (where sperm are produced) and Sertoli cells (which nourish developing sperm in the seminiferous tubules) decreases. Overall sperm production decreases, and the number of abnormal sperm increases [21]. These changes in testicular function tend to occur slowly.

Testosterone levels in older men are usually mildly low, resulting in decreased strength, cognitive functioning, bone density, and sexual function, and increased frailty and fractures. Among frail older men, testosterone deficiency is more marked, and as much as 45% of male nursing home residents may have hypogonadism, which is not a feature of healthy aging [21]. It is thought that central obesity may also contribute to lower testosterone levels and that, in some, weight loss may help to correct testosterone levels [21].

4.6.5 Adrenal Glands

4.6.5.1 Cortisol Production

The hypothalamic-pituitary-adrenal axis becomes overactive over time, increasing cortisol levels [20]. It is hypothesized that increased adipose tissue results in greater conversion of corticosterone to cortisol. The aging body also clears cortisol more slowly. In older adults, stress causes cortisol to peak at higher levels and remain elevated for longer [21]. Increased levels of cortisol may cause muscle wasting, frailty, physical disability, cognitive impairment, increased obesity, insulin resistance, and decreased immune function [20].

4.6.5.2 Renin-Angiotensin-Aldosterone System

Due to the decline of the renin-aldosterone-angiotensin (RAA) system, the body produces less angiotensin, decreasing renin by 50% and aldosterone by 30% in older adults compared to younger adults [21]. The body is less able to mount an appropriate response to low sodium levels or orthostatic hypotension as the RAA system declines.

Sympathetic receptors lose sensitivity over time, rendering older persons at higher risk of orthostatic hypotension [20]. For instance, the aging heart may not be able to strengthen contractions in response to hypoxia. Stimulation of alpha-adrenergic receptors may result in less vasoconstriction.

4.6.6 Osteoporosis

Vitamin D promotes the absorption of calcium from the small intestine. However, aging kidneys produce less vitamin D. The intestines also become less sensitive to Vitamin D and thus absorb less calcium. As a result of decreased calcium levels, parathyroid hormone (PTH) increases. PTH indirectly stimulates osteoclasts to release calcium from the bone to compensate for decreased calcium levels and, in so doing, lowers bone density.

In women, estrogen acts on receptors in osteoblasts and osteoclasts to repress bone turnover. Lower estrogen levels in older women cause decreased inhibition of bone turnover, increased bone loss, and greater risk of osteoporosis. Decreasing levels of estrogen in older men also predict age-related bone loss [22] (Table 4.6).

Table 4.6 Aging of the endocrine system

Glands	Age-associated changes	Possible consequences
Pineal gland	↓ Circadian rhythm of melatonin	Insomnia
Thyroid	Atrophy ↑ Fibrosis and nodule formation	↑ Rate of hypo- and hyperthyroidism
Parathyroid glands	↑ Parathyroid hormone (PTH) ↓ 1,25 (OH) Vitamin D levels Changes in bone mineral homeostasis	Vitamin D deficiency Osteoporosis
Adrenal glands	↓ Aldosterone secretion	Orthostatic hypotension
Female gonads	↓ Estrogen	Menopause Bone loss
Male gonads	↓ DHEA, DHEA-S, and testosterone levels Changes in diurnal rhythm	Changes in skin, hair, muscle, and bone

4.7 Aging of the Nervous System

Healthy older adults may experience mild cognitive and sensorimotor deficits. Mobility, coordination, and strength may decrease. However, the presence of more significant deficits may signify neurologic disease, such as stroke, Parkinson's disease, or Alzheimer disease, all of which are more common among older adults. Thorough neurological exam and assessment of baseline mental status are crucial in order to differentiate between changes associated with healthy aging and pathology.

4.7.1 Central Nervous System

The aging brain undergoes a number of changes. Brain mass decreases (Fig. 4.6). Brain neuron membranes also stiffen. Neurofibrils (filaments) and lipofuscin (lipid pigment that represents wear and tear) deposit in the neurons. Baroreceptors that help maintain blood flow to the brain deteriorate. Due to these changes, nutrient supply to the nerves wanes, and nerve impulses slow.

Cognitive changes of normal aging include decreases in cognitive flexibility, visual-spatial perception, working memory, and attention span [23]. The ability to learn does stay intact; however, processing speed decreases over time [4]. The response time of an older adult is about 1.5 times slower than that of a younger adult [24]. Executive functioning and working memory also deteriorate, particularly after age 70 [4].

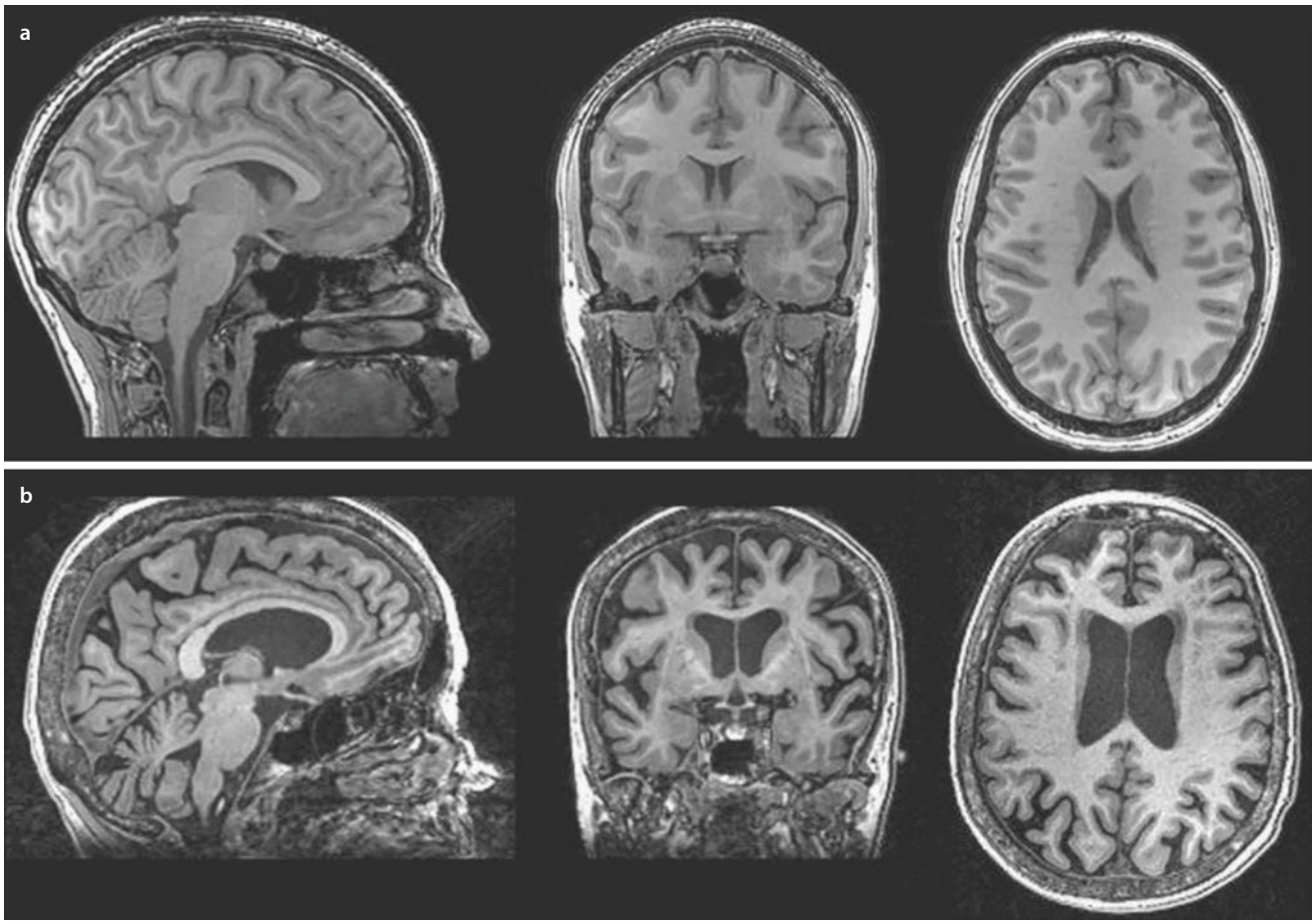

Fig. 4.6 Shows decreasing volume of human brain over time. **a** Magnetic resonance imaging (MRI) sections from a healthy 24-year-old woman. **b** MRI images of brain from a healthy 80-year-old woman without dementia (mini-mental status examination 30). Note the brain atrophy, larger sulci, and ventricles and different shapes of the ventricles due to brain tissue loss. (Reprinted with permission from: Halter et al. [30])

Other factors, such as fatigue, stress, medications, delirium, and depression, also compromise cognitive function. Decreased cognitive function often entails loss of independence for the older adult.

4.7.2 Peripheral Nervous System

Autonomic dysfunction may occur due to failure of the peripheral nervous system or the presence of comorbidities such as diabetes. Autonomic dysfunction may result in urinary retention or incontinence, constipation, impotence, gastroparesis, or anhidrosis (absence of sweating) [25]. Autonomic failure also thwarts the body's blood pressure regulation system, leading to orthostasis and increased risks of falls.

The number of spinal neurons decreases, and spinal nerve conduction slows, resulting in delayed transmission of sensory information, slowed motor movements, and prolonged response times (Table 4.7).

Table 4.7 Aging of the nervous system

Central nervous system (CNS)	
Age-associated changes	*Possible consequences*
↓ Brain weight ↓ Cerebral blood flow ↓ Number and functioning of CNS neurons ↑ Neurofibrillary tangles and lipofuscin Altered neurotransmitters	Slower processing speed → tasks take longer to perform ↓ Cognitive flexibility ↓ Visual-spatial perception ↓ Working memory ↓ Attention span
Peripheral nervous system	
Age-associated changes	*Possible consequences*
↓ Spinal motor neurons Nerve conduction slows	Delayed transmission of sensory information Slowed motor movements Delayed response times

Fig. 4.7 **a** Normal vision. **b** Blurry vision due to cataracts. **c** Loss of peripheral vision, leading to "tunnel-like" vision, due to glaucoma. (Reprinted with permission from: National Eye Institute, National Institutes of Health [32, 33])

4.8 Sensory Changes of Aging

4.8.1 Sight

Changes in vision occur due to structural changes of the aging eye. Pupil size shrinks (senile miosis), and pupillary reflexes lag, requiring more time to constrict and dilate and slowing responses to changes in lighting and glare. The number of photoreceptors decreases, leading to compromised visual acuity, particularly when lighting is dim or scarce. This is why older people often have difficulty driving at night. With age, people lose the ability to gaze upward and may have difficulty seeing traffic lights and street signs [23].

The lenses of the eyes stiffen due to the constant formation of epithelial cells at the lens, causing both blurry vision and presbyopia (loss of nearsightedness). This is why more older adults need reading glasses.

Cataracts (opacification of the lens), glaucoma (increased intraocular pressure), and macular degeneration (deterioration of the macula of the retina) are more frequent in the older population and also contribute to compromised visual acuity (Fig. 4.7). Diabetes and hypertension, both common among older people, affect the blood vessels of the retina, further distorting vision.

Hearing loss in the elderly is known as presbycusis. Older people may acquire sensorineural hearing loss and decreased auditory acuity for high-frequency sounds due to loss of cochlear hair cells and stiffening of the ossicles. Loss of high-frequency sounds compromises their ability to comprehend speech. Older adults may also develop conductive hearing loss and decreased auditory acuity for low-frequency sounds due to thickening of the eardrum.

4.8.2 Smell and Taste

The senses of smell and taste wane with age. Older adults have greater difficulty distinguishing between different odors. Decreased sense of smell may be due to anatomical changes of the upper airway or the olfactory nerve. Alzheimer and Parkinson's diseases are both associated with decreased smell [23]. Taste lessens as the sense of smell and the number and sensitivity of taste buds decline [14]. This may partially account for diminished appetite among older adults, causing weight loss and malnutrition.

4.8.3 Vibration and Proprioception

Older adults have a decreased sense of vibration and proprioception, both of which depend on the dorsal column of the spinal cord. The decline in these senses may be due to degen-

Table 4.8 Aging of the senses

Changes in vision	
Age-associated changes	*Possible consequences*
↓ Pupil diameter Slowed pupillary reflexes ↓ Number of photoreceptors	↓ Visual acuity
↑ Lens rigidity due to formation of central epithelial cells at the front of lens	Inability to focus on near objects (Presbyopia) ↓ Visual acuity
Changes in hearing	
Age-associated changes	*Possible consequences*
↓ Number of cochlear hair cells ↓ Stiffening of ossicles	↑ Sensorineural hearing loss (high-frequency sounds)
Thickened eardrum	↑ Conductive deafness (low-frequency range)
Changes in smell	
Age-associated changes	*Possible consequences*
↓ Sense of smell	↓ Ability to enjoy food ↓ Appetite, leading to potential weight loss
Changes in taste	
Age-associated changes	*Possible consequences*
↓ Number and sensitivity of taste buds	↓ Taste Weight loss Malnutrition

erative changes in the dorsal column nerve fibers and atherosclerosis of arteries supplying the dorsal column. Due to decreased proprioception, older adults may have a mild sway on the Romberg test, increasing their risk for falls [23] (Table 4.8).

4.9 Aging of the Musculoskeletal System

4.9.1 Muscle

Muscle mass decreases over time. This loss in muscle mass among older adults is called sarcopenia. It is especially common in the hands, feet, and shoulders and occurs due to the loss of muscle fibers and infiltration of fat cells. The weakening of abdominal muscles may exacerbate lumbar lordosis (abnormal inward curve of the lower back) and low back pain and increase the risk of umbilical and inguinal hernias.

Older people move more slowly. One study found that older people tap their hands and feet 20% more slowly [23]. Another study found that Parkinsonian signs, such as rigidity, bradykinesia, tremor, and gait disturbance, were present in 14.9% of those 65–74 years of age and in 52.4% of those

Table 4.9 Aging of the musculoskeletal system

Components of musculoskeletal system	Age-associated changes	Possible disease outcomes
Muscle	↓ Muscle fibers → ↓ Muscle mass (sarcopenia) Infiltration of fat into muscle	Weakness Lumbar lordosis (abnormal inward curve of the low back) ↓ Mobility ↓ Functional independence
Bone	↓ Number of osteoblasts ↓ Vitamin D → ↓ Calcium levels → ↓ Bone formation ↑ Bone loss	Osteoporosis Kyphosis Loss of height
Joints	↓ Thickness of cartilage ↓ Chondrocytes	Osteoarthritis

85 years of age or older. These symptoms hinder the ability to perform activities of daily living, such as dressing and eating.

Older people have greater difficulty with balance and maintaining an upright posture, both of which are needed for a steady gait. Gait instability increases the risk of mortality twofold [23].

Older adults fall more often and have a higher risk of hip fracture due to increased bone fragility. Hip fractures are associated with increased morbidity and mortality, and many older people do not return to their prior level of functioning after a hip fracture.

4.9.2 Bone

Bone loss starts at about 35–40 years of age for both women and men as the number of osteoblasts (cells that produce bone) decreases [22]. Decreased weight-bearing exercise and vitamin D deficiency also contribute to bone loss. In postmenopausal women, lower levels of estrogen exacerbate this bone loss. Bone loss increases the risk for osteoporosis.

Height decreases because intervertebral discs lose fluid and vertebrae lose mineral content, shortening the spinal column and causing posture to become stooped [7].

4.9.3 Cartilage

Friction causes cartilage in the joints to erode, leading to osteoarthritis [7]. Chondrocytes (cells that regenerate cartilage) also decrease over time. Joint cartilage never regenerates (Table 4.9).

4.10 Aging of the Skin

Skin atrophies with age. Wrinkles form and skin sags due to loss of skin elasticity from increased collagen and decreased elastin. Skin may become paler and hair becomes gray because melanocytes dwindle. Hair thins due to decreased hair follicles [7].

Understanding the layers of the skin is important in order to understand how the skin ages. The skin consists of two layers as well as a basement membrane:

1. Epidermis, the outer layer
2. Dermis, the inner layer
3. Dermo-epidermal junction, basement membrane that connects the epidermis and dermis

The epidermis and the dermo-epidermal junction thin, making the skin more fragile and susceptible to shear stress. Taking off an adhesive bandage may result in skin tears in older adults as the adhesiveness of the bandage is stronger than the bond between the epidermis and the dermo-epidermal junction. Bleeding between the epidermis and dermis also becomes more common [4].

Because the dermo-epidermal junction loses its unevenness, there is less surface area for nutrient exchange, leading to xerosis (dry skin). Blood vessels in the dermis decrease, delaying and altering wound healing, which may lead to chronic ulcers. Dendritic cells (antigen-presenting cells that stimulate the immune system to help repair cells) malfunction, increasing risk for skin cancer [26].

Thermoregulation of the skin also decreases, making older people more susceptible to cold.

Photoaging, which occurs due to exposure to UV rays, results in skin yellowing, wrinkles, and hyperpigmentation (called lentigines, or sun spots) or hypopigmentation. Due to the loss of melanocytes and melanin in the skin, aging skin has less protection against UV rays and becomes more susceptible to skin cancers [27].

Immobility in the older adult increases susceptibility to pressure ulcers and wound infections (Table 4.10).

Table 4.10 Aging of the skin

Changes in structure	
Age-associated changes	*Possible consequences*
↓ Melanocytes ↑ Lentigines (sun spots) Epidermis thins	Pale skin ↑ Susceptibility to skin tears Skin cancer
Dermal changes ↑ Collagen ↓ Elastin	Wrinkles Lax skin
↓ Melanocytes at base of hair follicles	Gray hair
Changes in function	
Age-associated changes	*Possible consequences*
↓ Effectiveness of thermoregulation	Vulnerability to heat and cold
Impaired wound healing	Chronic ulcers Persistent wounds

4.11 Aging of the Immune System

Due to immune senescence (the process of immune system aging), an older person is less able to protect against infection and malignancy. Poor nutrition, poor dentition, muscle atrophy, dementia, and polypharmacy compromise the ability of an older person to compensate for infection. The number of autoimmune cells increases, weakening the immune system and increasing the prevalence of autoimmune diseases.

4.11.1 T Cells

The thymus is an organ in the mediastinum that produces T cells, a type of lymphocyte or white blood cell. With age, the thymus atrophies. The production of naïve T cells decreases, increasing susceptibility to new infections. The thymus also produces fewer natural killer cells and fewer of the cytokines essential for the growth and maturation of B cells (lymphocytes that produce antibodies). There is also an expansion of differentiated T cells, resulting in a more homogenous and less versatile T-cell population. Decreased ability to repair DNA damage and combat oxidants increases cancer risk.

4.11.2 B Cells

Like T cells, there is a decreased production of naïve B cells and expansion of antigen-differentiated B cells, resulting in a smaller and less diverse B-cell population. This results in a declining antibody response to vaccinations and foreign antigens, such as microbes. The formation of germinal centers, which are B-cell-producing factories, also decreases over time. Due to immune system dysregulation, production of autoimmune antibodies increases and may underlie the higher prevalence of autoimmune disease in older adults [4].

After receiving the influenza vaccine, 70–90% of people younger than 65 years of age are protected; however, only 10–30% of older frail adults are protected due to the aging of the immune system [28].

All of these changes mean that an aging immune system is less able to defend against infections. Influenza, pneumococcal pneumonia, and urinary tract infections become more common. Older adults manifest atypical presentations of infections. A subtle change in mental status or behavior, loss of appetite, falls, incontinence, or fatigue may be the only signs of an infection. Signs, such as leukocytosis or fevers, may not be present in the older adult with an infection because the immune system is less able to mount a response to foreign antigens (Table 4.11).

Table 4.11 Aging of the immune system

Age-associated changes	Possible consequences
↑ Autoimmune antibodies	↓ Immune functioning ↑ Autoimmune disease
↓ T-cell function ↓ Naïve cells ↑ Differentiated T cells	↓ Response to new pathogens ↑ Susceptibility to infection ↑ Susceptibility to malignancy
Atrophy of thymus → ↓ T cells, natural killer cells	↑ Susceptibility to infection ↑ Susceptibility to malignancy

Table 4.12 Aging of the hematological system

Age-associated changes	Possible consequences
↓ Hematopoietic tissue in bone marrow	Anemia
↑ Fat infiltration of bone marrow	Myelodysplastic syndrome
↓ Stem cells in bone marrow	Leukemia
↓ Incorporation of iron into RBC → slowed erythropoiesis	
↓ (slightly) Average hemoglobin/ hematocrit	

4.12 Aging of the Hematological System

Stem cells and hematopoietic tissue in the bone marrow diminish as fat takes their place. Infiltrated by fat, the bone marrow is less able to regenerate blood cells. Greater amounts of iron are incorporated into red blood cells, slowing erythropoiesis. Consequently, the average hemoglobin and hematocrit of the older patient decreases slightly. The prevalence of anemia in the elderly may also be due to inflammation, hence the term anemia of chronic disease.

Damaged DNA increases with age perhaps both due to increased reactive oxygen species (ROS) and malfunction of DNA repair mechanisms, contributing to the risk of hematologic malignancy. Shortening of telomeres, the end section of chromosomal DNA, may also contribute to bone marrow failure [28]. Bone marrow failure leads to myelodysplastic syndromes (MDS). The hallmarks of myelodysplastic syndromes (MDS) include a diminished capacity to produce blood cells, progressive bone marrow failure, and risk of transformation to acute myeloid leukemia (AML) (Table 4.12).

4.13 Conclusion

It is important to recognize typical physiologic changes in aging as reviewed in this chapter and to be able to distinguish them from pathology in older adults. Toward that goal, the following chapters will describe disease in the older population.

Learning to care for a vulnerable population of older adults offers unique challenges and rewards. We hope this textbook will serve as a reference for you as you learn more about this population.

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