Course: Physiology and Pathophysiology

Study: Cosmetology

Form of classes and number of hours: lectures 30 h + 15 h, laboratory classes 30 h + 15 h

Number of ECTS credits: 3+3

Educational outcomes:

- knowledge of the basic mechanisms in physiology,
- the basics of metabolism,
- knowledge of the basics of the physiology of individual systems,
- broader knowledge of the physiology of the skin

The method of verification of the learning outcomes:
examination

Subject matter of the classes:

1. Basic concepts in physiology.
2. Basic energy metabolism.
3. Protein, carbohydrate and lipid metabolisms.
4. An outline of the physiology and pathophysiology of the nervous system.
5. Musculoskeletal system, cardiovascular system, respiratory system, digestive system.
6. Hormonal regulations.
7. Electrolyte and acid-base balance.
8. Reproductive physiology.
9. Mechanisms of inflammation.
10. Detailed skin physiology – this part is included in the following text.

Bibliography

Books

Błaszczyk M., *Fizjologia skóry* [in:] A. Kołodziejczak, *Kosmetologia*. PZWL, 2019.

Silverthorn Dee U., *Human Physiology: An Integrated Approach*. Pearson Education, 2014.

Widmaier E., *Vander's Human Physiology*. Mc Graw Hill, 2015.

Westley A., *Human Physiology*. Larsen and Keller Education, 2019.

SKIN PHYSIOLOGY

Physiology is an extremely complex science. In the field of Cosmetology, it covers a brief outline of the selected part of issues in this field, and in the present text only selected issues concerning the physiological mechanisms characteristic for the skin are mentioned.

1. Skin metabolism

1.1. Hormonal regulation of skin functions

Hormones are substances secreted by one cell that affect the metabolism of target cells. Among the hormones, sex hormones, estrogens (estradiol, estriol and estrone) and androgens (especially testosterone) have the most explicit effect on skin functions in various physiological states. Both of these hormone groups in a great extent share a common metabolic synthesis pathway. The precursor is dehydroepiandrosterone (DHEA), with weak androgenic activity. Both of them and androstenedione, its metabolite, can then be metabolized into testosterone and then into dihydrotestosterone or into estradiol, i.e. estrogen.

Androgens and estrogens are commonly known as male and female hormones, respectively. However, both of these groups of hormones are present in both sexes, only their proportion changes. Conversion to dihydrotestosterone occurs rather in men, to oestradiol rather in women. The function of white adipose tissue is extremely important here: it can be converted to estradiol. Therefore, women having deficiency of adipose tissue can have cycle disorders (and even disappearing cycles) and fertility disorders. On the other hand, high physical activity, apart from the cycle disorders, may lead to an increase in the level of androgens. Hirsutism and virilism are often observed in women practicing demanding sports.

Estrogen receptors are ERα receptors (they are located in the skin mainly in the nipples of hair bulbs and in sebaceous glands, less in sweat eccrine glands), and ERβ (in dermal fibroblasts, adipocytes of adipose tissue, epidermal keratinocytes, and also in the places where ERα receptors occur).

Androgen receptors (AR) exist at sites similar to ERα receptors. They are very similar to progesterone receptors. Like ER receptors, they are a DNA-binding transcription factor. This location of receptors for sex hormones gives us an idea of the functions regulated by the hormones and explains the different phenomena observed in both sexes, occurring at different stages of life. Hormone levels of both sexes are similar to those in puberty period, when the secretory activity of the ovaries and testes increases. Under the influence of estrogens or androgens in both sexes, characteristic changes in the appearance and functioning of tissues occur, for example, the expansion of adipose tissue in specific locations in women, changes in skin thickness, changes in body hair, changes in the functions of the sebaceous glands. The high level of androgens later determines androgenetic alopecia in men. In women during pregnancy, the level of estrogen increases, under the influence of which the anagen stage (hair growth) is extended and it improves hair density. However, after pregnancy, the level of prolactin increases significantly (due to milk production), and the level of estrogen decreases, the hair follicles enter catagen phase, i.e. hair thinning.

With age, the level of sex hormones decreases markedly. In men, this applies especially to DHEA, it is a decrease to a level of several percent of the maximum value. Testosterone levels decline more slowly, by about 1% per year, which results, among others, in a decrease in the anabolic effect on muscle tissue, a decrease in the activity of the sebaceous glands (although not in their size). In women, the decline in sex hormone levels is much more drastic, so it is more noticeable after the men-

opause. Then, the balance between androgens and estrogens is disturbed, hair thinning and acne are observed, and the distribution of adipose tissue changes (abdominal adipose tissue is under the control of androgens, subcutaneous tissue of the face – rather estrogens). It is estimated that in the 5 years after menopause, the level of collagen synthesis drops by 30%, and then by another 2% each year. GAG synthesis is likewise decreased. These changes are perceived as a reduction in the elasticity, strength and hydration of the skin, and worsening the wound healing process.

Now, the hormones also include growth factors. They are proteins or steroid hormones. From the point of view of cosmetology and dermatology, it can be assumed that in the future the following may be used: Fibroblast Growth Factor (FGF), keratinocite GF (KGF), Epidermal GF (EGF), and Vascular Endothelial growth factor (VEGF). FGF1-2 initiate the proliferation of blood vessel epithelia and their organisation into "tubes". They show a stronger effect than VEGF. They work similarly in the case of wound healing. FGF7 and 10 (also known as KGF – keratinocyte growth factor) enhance the multiplication, migration and differentiation of epithelial cells. Most of the FGFs bind to heparan sulfate in the dermis. TGF is Transforming growth factor, or Tumor GF, is the joint term for TGFα and TGFβ. These are two completely different growth factors, structured and acting by different receptors. The name comes from the fact that they are factors that may (but does not have to) cause neoplastic transformation of target cells. Generally, TGF stimulates the development of epithelia. EGF, or epithelial growth factor, promotes cell differentiation and growth after binding to the EGFR receptor.

1.2. Skin as an immune organ

Due to the location of the skin (part of the body outer covering), it is one of the elements of the anti-infection system. By creating a mechanical barrier (keratinized epidermis with a thick basement membrane) and a chemical barrier (including low pH), it also contains cells that actively participate in the immune response.

Here, physiology covers topics relating to general mechanisms of inflammation, cells involved in inflammatory responses and inflammatory mediators. Due to space limit, these topics will only be highlighted, with an emphasis on the unique skin mechanisms.

Cells that implement the mechanisms of inflammation include, among others, mast cells, macrophages, neutrophils, basophils, eosinophils, T and B lymphocytes. The skin also contains epidermal cells: keratinocytes, melanocytes, especially Langerhans cells, and fibrocytes / fibroblasts of the dermis. For example, Langerhans cells function as antigen presenting cells.

These cells synthesize inflammatory mediators that regulate its course. They include, for example, cytokines (anti-inflammatory – TGFβ, IL-10, and pro-inflammatory), lipid mediators (prostaglandins, prostacyclin, thromboxane A, leukotrienes, lipoxins), neuropeptides, biogenic amines, HMGB1, plasma mediators (complement system, fibrinolysis, and kinin). In the skin, these substances can undergo unique mechanisms. For example, the anti-inflammatory interleukin IL-10 is produced in higher concentrations in keratinocytes under the influence of UV radiation, which has an immunosuppressive effect, limiting tissue damage from inflammatory responses. The skin has specific growth factors, also classified as inflammatory mediators.

The cells involved in immune responses have an oxygen-dependent and an oxygen-independent killing mechanism for bacteria. In the case of the former, the factor destroying cell structures are reactive oxygen and nitrogen species. These include: superoxide anion O^{2-}, hydroxyl radicals, atomic oxygen, H_2O_2, synthesized in the vascular endothelium and neurons, and in macrophages. Reactive oxygen species destroy cell membranes and other microbial structures.

Oxygen-independent mechanisms cover several groups of substances. They include, among others lysosomal enzymes, glycosidases (including lysozyme), proteases, destroying bacterial walls and

membranes, defensins disrupting the functions of cell membranes, lactoferrin disrupting bacterial metabolism by eliminating iron from the environment.

The skin lymphatic system is so complex that it constitutes a separate part of the immune system – SALT (skin-associated lymphoid tissue), which belongs to a part of MALT (mucosa-associated lymphoid tissue, which constitutes half of the body's lymphatic tissues).

The course of inflammatory responses itself will not be discussed here. However, it should be emphasised, that these responses are a necessary evil for the body. By protecting against infections, they damage connective tissues, including the skin. The consequence is the acceleration of skin aging ('aging' in terms of degradation, impairment of structure and function). The cells involved in inflammatory responses produce substances that destroy the structures of connective tissues, often deliberately directed to do so (enzymes that destroy the fibers of connective tissues to facilitate migration of these cells). Multiple or chronic inflammations lead to irreversible changes in connective tissues. When the topic of extrinsic factors accelerating skin aging is raised in cosmetology, the emphasis is made on ultraviolet light and smoking. They affect the tissues mainly through reactive oxygen species and the immune system. Under the influence of ultraviolet, the inflammatory process associated with skin burns develops during sunbathing, pro-inflammatory interleukins IL-1, IL-6 and IL-8 are generated. They stimulate the production of reactive oxygen species by macrophages and neutrophils. TGFα enhances cell multipli-cation, TNF inhibits it, and this modulates cell division in the epidermis, and at the same time affects pigmentation disorders, affecting melanocytes. UV causes an increase in the activity of the AP-1 protein, which increases the expression of genes encoding matrix metalloproteinases (MMP). Metallo-proteinases degrade the fibers of connective tissues, including the skin.

During aging, the skin's immune activity decreases. This is inter alia, due to the decreased activity of toll-like receptors, especially TLR1. There is also an increase in the secretion of the anti-inflammatory interleukin IL-10. This leads to an increased susceptibility to infections in old age.

On the other hand, toll-like receptors also affect the synthesis of metalloproteinases (degrading collagen and other skin proteins), and reducing the severity of inflammatory reactions reduces tissue damage.

With age, the density of TGF receptors and their activity decrease. TGF stimulates proliferation, so the effect of these changes is to slow down the multiplication of cells (renewal of the epidermis), slowing down the wound healing process. It also has the advantage: TGF stimulates cancer formation, which is why older people are less likely to develop some types of cancer than younger people.

It is worth mentioning here about the risky experiments of cosmetics producers. Trying to patent and sell something new, they reached for growth factors, including TGFβ. Theoretically, it should stimulate tissue regeneration processes, stimulate fibroblasts, macrophages, leukocytes, and keratinocytes. First of all, no efficacy of these cosmetics has been observed, it has never been demonstrated in scientific studies (manufacturers' 'research' cannot be taken into account, of course). Secondly, the use of TGF under laboratory conditions most often leads to the development of tumors. TGF stands for '*transforming growth factor'*, but for good reason, the abbreviation '*tumor growth factor'* is often used.

Speaking about inflammatory and cancer mediators, it can also be mentioned that UV, which can damage DNA, at the same time protects against cancer in many ways, including increasing the level of TNF and vitamin D. This vitamin protects against microorganisms and cancer thanks to the fact that lymphocytes T need to bind to the active form of vitamin D, calcitriol, in order to be active against microorganisms and cancer cells. Without vitamin D, T cells are inactive. Therefore, the T cells themselves promote the conversion of calcidiol (inactive form) to calcitriol through the

expression of the CYP27B1 gene. Also keratinocytes show a similar activity. It is known that only in the presence of UV vitamin D is formed in the skin. Its absorption from the gastrointestinal tract is quite limited. There are more and more review publications proving that people who avoid UV exposure are more likely to develop cancer.

1.3. The function of the skin in the water and electrolyte balance

Supplied and wasted water must reach a balance. According to various estimates, for an average adult person, the amount of water changed during the day is about 2-2.4 liters. 0.3 liters is metabolic water (produced by chemical reactions in tissues). The remaining 1.7-2.1 litres should therefore be consumed, about 0.9 liters with solids, about 0.8-1.2 liters with liquids. Water intake is in balance with water loss by evaporation (through skin and lungs 0.9 liters in total), 0.1 liter in faeces, 1-1.4 liters in urine. If the body overheats due to external or internal thermal stress, loss of water with sweat must be added. Sweating is regulated by the autonomic system and it is exacerbated in two situations: overheating and emotional tension (limited to the hands, feet, armpits and forehead). In addition to urea, citric acid, ascorbic acid and lactic acid, i.e. organic substances, sweat contains water, sodium (approximately 0.9 grams/liter), potassium (0.2 g/l), calcium (0.015 g/l) and magnesium (0.0013 g/l), chloride anions, as well as zinc, copper, iron, chromium and nickel in trace amounts, but also the concentration of these metals in the plasma is minimal. So it is clear that sweating must play a significant role not only in the body's water balance but also in the body's electrolyte balance. Additionally, vitamin D is synthesized in the skin under the influence of UVB, which determines the intestinal absorption of calcium, magnesium and phosphate anions. The function of the skin as the body's water barrier will be discussed later.

1.4. Lipid metabolism

Lipids in the body are the basic energy storage material, the lipids are stored in adipose tissue. Depending on the needs, they can be deposited in or released from adipose tissue. Lipogenesis is the synthesis of lipids, lipolysis is their breakdown.

Fatty acid synthase (FAS) is a group of massive enzymes that carry out the acetyl-CoA and malonyl-CoA condensation reactions in which the two-carbon fragments gradually extend the fatty acid chain. Regulation of FAS activity is achieved by enhancing or inhibiting transcription by regulatory factors (*Upstream stimulatory Factors* and *sterol regulators element-binding protein*, SREBP), which in turn are stimulated by food intake and changes in insulin levels. Fatty acid synthesis takes place mainly in the cytoplasm of adipose tissue and liver.

Fatty acid degradation is β-oxidation, a mitochondrial process that cleaves the higher fatty acid chains into two-carbon pieces.

Several hormones regulate the balance of lipid metabolism. They include leptin and insulin. The increase in insulin level associated with the increase in blood glucose levels increases the absorption of free fatty acids by cells. Increasing the level of insulin also increases the transport of glucose inside the cells, where glycogen can be produced from it, or – especially in adipose tissue – fatty acids and lipids. Leptin, in turn, inhibits the absorption of fatty acids into cells and reduces the expression of genes related to lipid synthesis. Other hormones are triiodothyronine and thyroxine, they increase fatty acid catabolism. Glucocorticoids of the adrenal cortex – cortisol and corticosterone – act in a similar way, increasing the breakdown and oxidation of lipids, increasing the level of free fatty acids in the plasma, up to a ketogenic effect.

The neuronal factor regulating the metabolism of adipose tissue is the degree of stimulation of the autonomic system, mainly the level of norepinephrine (the neurotransmitter of the sympathetic system). Stimulation of α-adrenergic receptors reduces lipolysis, stimulation of β-adrenergic receptors enhances lipolysis.

1.5. The skin's mineral balance

Details of the role of individual minerals will not be discussed here, the skin shows no difference to other tissues. However, it is worth emphasizing the role of the elements necessary for the functioning of metalloproteinases, which have a decisive impact on the condition and aging of the skin. Most often it is zinc, sometimes, it is cobalt. In the old age, zinc supplementation could be justified. In addition to metalloproteinases, it is essential in the molecules of superoxide dismutase, lactate dehydrogenase, alkaline phosphatase, carbonate dehydratase, etc. As a result, it has an indirect, anti-inflammatory effect, improves the epidermal barrier function, and accelerates wound healing. In general, supplementation (besides the exceptional clinical cases) is never necessary, but zinc levels decline with age.

It has also been suggested that adequate levels of calcium, phosphorus, iron, zinc and magnesium can reduce the effects of photoaging. However, it should be emphasized again here that in an average diet the amount of these elements is sufficient and there is no need for supplementation.

A very controversial microelement is silicon. It is known to be present in trace amounts in connective tissues. There is a centuries-old belief in the public mind, and a lot of publications linking silicon to the condition of the skin, hair and nails. It is claimed that it is critical to collagen synthesis, wound healing, etc. However, there is no serious study that meets the standards of scientific research confirming these theses. There is -any known mechanism of action based on silicon, it is not a coenzyme, such as zinc, nickel, magnesium, manganese, molybdenum, iron, cobalt.

2. The role of the skin in thermoregulation

Humans are warm-blooded animals. Body temperature is controlled by a thermoregulation center located in the diencephalon, in the hypothalamus. In its front part there is a heat elimination center, in the rear part – heat preservation. The stimulation or inhibition of these centers triggers the reaction of thermoregulatory effectors, aimed at increasing heat loss or saving.

Information about temperature changes reaches the thermoregulation center from thermoreceptors, which are located in the skin, and inside the body in the muscles, upper respiratory tract, vein walls, gastrointestinal walls, and in the central nervous system.

There are a lot of mechanisms and effectors of thermoregulation, but only those related to the skin will be mentioned here. They are related to passive thermal insulation, as well as to the skin's blood flow and sweating.

Saving heat is possible thanks to the characteristic blood supply to the skin. Each dermal papilla is reached by an artery that supplies warm blood, which when cooler, returns through the vain. The veins here are parallel to the arterioles. Thanks to this, part of the heat supplied by the arteriole is immediately transferred to the blood that returns through the vein, without reaching the outermost (coolest) parts of the papilla.

When we are cold, the blood vessels narrow in the skin (under the influence of epinephrine or noradrenaline of the sympathetic nervous system, acting on the adrenergic receptors of the smooth muscle of the blood vessels, causing them to contract), the flow of warm blood in the skin decreases, so heat is saved. However, if it is very cold, ischemia and frostbite may result. Therefore, at low temperatures, the sensitivity of α-adrenergic receptors decreases, so the muscles do not contract, and the vessels dilate.

In the case of humans, piloerection does not matter – the vellus hair is too delicate to maintain a thermally insulating layer of the air.

In turn, the elimination of heat, in the event of an excessive increase in temperature, is made possible by the expansion of the skin blood vessels, thanks to which the heat is radiated outside.

The second factor of thermoregulation related to the functioning of the skin is the evaporation of sweat. At temperatures above 32°C, normal (eccrine) sweat glands secrete water-rich sweat. Of course, just the release of sweat does not lower the temperature. Water from the surface of the body has to evaporate, i.e. it has to change its state from liquid to gas. A considerable amount of energy is required for this phase transition, as water has a very high heat of vaporization.

3. Skin pigment

In the basal layer of the epidermis there are melanocytes, cells of common origin with nerves, responsible for dye synthesis. Their protrusions reach the granular layer, where the dye is released and absorbing ultraviolet radiation, protects the DNA of the cell nuclei from damage.

The color of the skin, hair and iris is melanin. It is synthesized from the amino acid tyrosine, the first stages of synthesis are catalyzed by the enzyme called tyrosinase. The intermediate metabolite is DOPA-quinone, at this stage the pathways for the synthesis of two types of melanin (eumelanin and pheomelanin) separate.

The factor regulating melanin synthesis is the melanocyte-stimulating hormone (MSH) and the distribution and activity of its receptors. The color of the body is largely determined by genetic factors, for example the MC1R gene encodes a receptor for a melanocyte-stimulating hormone. The presence of one of the alleles of this gene causes the synthesis of melanin to shift towards pheomelanin, which will result in a phenotypic consequence of pale skin and red hair, as well as inability to get tanned. Excessive production of melanin, due to too effective protection against UV, reduces the synthesis of vitamin D3 in the dermis, which results in e.g. rickets. The skin color was traditionally determined by using the von Luschan scale, now rather spectrophotometric methods are used.

The color of the skin can change under the influence of external factors (diet, medications, radiation).

When exposed to ultraviolet radiation, the skin visibly gets darker. Sunbathing initially involves oxidation of melanin already present and its darkening in response to UVA radiation. The initial phase of sunbathing can lead to the activation of inflammatory mechanisms, then both UVA and UVB increase the amount of melanin through stimulation of the melanocyte-stimulating hormone (MSH). In the case of redheads (presence of a specific MC1R allele), this defense is absent because it is based on MSH. UV radiation simultaneously stimulates the p53 protein system and the synthesis of vitamin D3. Both of them are important in preventing cancer.

4. Skin receptors

The skin is located as the most external body part, so it must be equipped with numerous receptors informing about changes taking place in the environment. These receptors are divided into a lot of classes, including chemoreceptors, nociceptors, thermoreceptors, and mechano-receptors. The mechanoreceptors include free nerve endings, among which there are endings responsible for the feeling of touch, heat, cold, polymodal (reacting to more than one type of stimulus), slow, medium and fast adapting receptors. They can surround the hair follicles, they can also reach the granular layer of the epidermis. Other receptors are Merkel terminals that reach Merkel cells in the basal layer of the epidermis. Together, they form Merkel sensory bodies, located especially on

the fingertips, in the vicinity of the mammary glands and in the hair roots. Meissner bodies are located in the papilla of the dermis just below the basement membrane, on hairless surfaces: lips, hands, fingers, nipples, conjunctiva, in the papilla of the dermis, most of them are placed on the thick epidermis. They recognize light touch and low frequency vibrations (10-50 Hz). Pacini corpuscles are found in the skin and subcutaneous tissue, mainly on the fingertips. The stimulus specific to them is pressure and vibration (250 Hz). Ruffini corpuscles are located in the deeper layers of the skin and in the subcutaneous tissue. The stimulus is the displacement of collagen fibres associated with the receptor, in practice it is about stretching the tissue or putting pressure on it. Krause end bulbs are found in the dermis, mucous membranes of the mouth, tongue and subcutaneous tissue. They perceive information about vibrations and spatial position of the source of the stimulus.

5. Epidermal barrier and skin protective function

The epidermis is part of the outermost shell of the body that separates it from the outside environment. Therefore, it must be a barrier that prevents unfavorable factors (such as microorganisms) into the body, and at the same time retains the necessary substances (including water) in the body.

The skin is a mechanical barrier to the penetration of substances and microorganisms. Whether a given substance passes the epidermal barrier depends primarily on the size of the molecule. The limiting particle size is about 5.000 Daltons. For example, hyaluronic acid or collagen are the particles with a size of several hundred thousand Da, they cannot be absorbed (contrary to the clames of cosmetics manufacturers). These molecules should be lipid soluble because there is a lipid envelope between the keratinized cells. As a result, the penetration of substances is increased by e.g. detergents and surfactants, destroying the epidermal barrier and reducing the surface tension). Permeability is also increased by a high concentration of substances, as well as greater exposure time and temperature. The thickness of the epidermis is very important for permeability. Obviously, the poorest absorption will be on the soles of the feet and on the palm of the hand. The greatest absorption should be found in the hair follicles and skin glands (thinnest layer), but these areas are only about 0.5% of the skin surface, they are deep and they are filled with secretions.

Bacterial flora of the skin. The surface of the epidermis is supersaturated and covered with a hydrolipid coat (film), i.e. a mixture of water and lipids. It is produced from the secretions of the sweat and sebaceous glands which undergo bacterial metabolism.

This mixture includes: water, lactic acid, urea, ions (Na^+, K^+, Ca^{2+}, Mg^{2+}), triglycerides, free fatty acids, waxes, squalene, and metabolites of sebaceous gland cells. These substances together with dead epidermis shape the pH of the skin and are a breeding ground for microorganisms.

The natural flora (or microbiom) of the skin includes about 1000 species of bacteria and dozens of species of fungi. The species composition varies on the body surface and to large extent depends on the number and activity of the sweat and sebaceous glands. The *Actinobacteria*, including *Propionibacterium* are predominant on the face, neck, back, lower abdomen and feet. *Bacterioidetes* and *Proteobacteria* predominate on the limbs and chest, and *Staphylococcaceae* at the back of the foot in the bends of the limbs. *Cyanobacteria* occur in various parts of the body. Among the fungi, the most common are: *Candida albicans*, *Rhodotorula rubra*, *Trichosporon cutaneum, Aspergillus spp., Penicillium spp., Rhizopus sp., Microsporum gypseum*.

These species are considered to be symbiotic and often beneficial. For example, they compete with other species, limiting their development through the production of antibiotics. However, a lot of them are opportunistic pathogens that cause infections in immunocompromised states.

Microorganisms are responsible for the odor of the human body. Sweat, both eccrine and apocrine, and sebum, are odorless, but after several dozen minutes, under the influence of bacterial metabolism (mainly *Bacillus subtilis*, *Propionibacteria*), the easily perceptible substances (propionic acid, isovaleric acid) are formed.

The development of microorganisms is limited by the constant exfoliation of the *stratum corneum* where they undergo multiplication.

Skin pH. The reaction of the epidermis surface results from the composition of sebum and sweat (especially lactic acid), and the mixture of substances resulting from the breakdown of proteins and epithelial lipids, as well as metabolites of the bacterial flora of the skin. In practice, the pH is around 4.5-6.2, with men having a lower skin surface reaction than women. The benefit of a low skin surface pH is that if skin bacteria enter the body (e.g. through a wound), they will have difficulty to grow, as the pH inside the body is around 7.4 (blood pH).

Microbiological protection is guaranteed through the skin, also thanks to its immune functions, described earlier.

Epidermal water loss and water retention in the skin (hydration)

The skin is involved in the body's water management thanks to the existence of a water barrier and the secretion of sweat related to thermoregulation. In the literature the abbreviations EWL (*epidermal*/*evaporative water loss*) are often used, sometimes TEWL (*transepidermal water loss*) to denote (through) epidermal water loss. There are several independent mechanisms that are capable to retain water in the skin. The dermis includes, among others collagen (collagen fibres) and glycosaminoglycans (GAGs, the constituent of the matrix of intercellular material). After dissociation, these substances are polyanions that can bind large amounts of water. GAGs are of key importance as they bind up to a thousand times more water than their own weight.

The *natural moisturizing factor* (NMF) is present in the outermost layers of the epidermis (the *stratum corneum*). It is a mixture of hygroscopic substances that are products of filaggrin breakdown, one of the proteins of the cell envelope built up in the granular layer. So these are amino acids (a lot of histidine, arginine, glutamate) and their metabolites, urocaine (*trans*-urocaine), citrulline, pyroglutamic acid, lactic acid and urea. These elements moisturize the dermis and epidermis, i.e. they bind the water. However, this does not mean that they prevent water loss. It is rather about saturating the tissue with water.

The factors that prevent water loss are: the lipid coat of the granular layer and the sebum on the epidermis surface. The lipid envelope deposited outside the cells of the granular layer is made of hydrophobic, water-resistant and of a lipid nature substances. Similarly, the sebum produced by the sebaceous glands is hydrophobic and reduces water penetration.

Despite the existence of an epidermal barrier, 300 to 700 ml of water per day penetrates the epidermis by diffusion beyond the sweat glands and evaporates imperceptibly from the body surface.

6. Functions of skin appendages

Human hair, nails, sweat and sebaceous glands are the products of the epidermis. They perform functions that are sometimes only apparently obvious.

Hair functions. The hair is arranged on the surface of the skin in a regular pattern, at fairly regular intervals. The overwhelming majority of mammals have their skin covered with thick hair. In our species, hair loss (or rather the replacement of coarse, long hair with hair) occurred 3.3 million years ago, as a result of environmental changes. More efficient heat loss became necessary. Eye-

brows and eyelashes protect the eyes (against rain, sweat, dust). Nose and ear hair protects against dust. Hair in the armpits and perineum mechanically protects against abrasions and chafing, and along with the hair follicle on the entire body surface – supports thermo-regulation by retaining sweat and allowing it to evaporate. Long hair on the head has no obvious function. It was once suggested that they protect the scalp from UV radiation coming from the zenith (the evolution of our species took place initially in Africa), which, in turn, contradicts the lack of hair on the shoulders, feet, etc. Currently, it is believed that leaving long hair on the head is related to sexual selection. If a person's diet is proper and he/she is in a good shape, hair grow smooth, shiny, unchanged along its entire length. However, in case of poor nutrition and if pathological conditions are present – the hair during this period will grow dull, uneven. Thanks to this, it is possible to recognize at first glance whether a given individual has done well in recent years, or whether it gives hope for raising a healthy child. Another function of hair is to help in sensation (the nerve endings around the hair follicle).

Nail functions. They protect the upper, distal part of the fingers. They make it possible to extract the edible parts of plants – roots, to tear their tissues and the tissues of hunted animals, they facilitate getting rid of parasites by scratching and brushing (note that these are the functions to which the organ has evolved, they are not artificially added currently).

Functions of the sweat glands. The basic functions of normal (eccrine) sweat glands are participation in thermoregulation and water and electrolyte balance, and they are also marginally responsible for clearing metabolic waste.

The apocrine (odorous) sweat glands have, or rather should have, a social function. Thanks to the smell specific to the species, sex and individual, animals recognize each other, manifest their social position, attitude and emotions.

Functions of the sebaceous glands. The tallow oils the hair, sticking the outer cells of the true hair coat together, which makes them smooth, flexible and resistant to weather conditions. When mixed with sweat, the tallow forms a layer that covers the skin. The hydrolipid film greases the epidermis, gives it elasticity, clumps exfoliating epidermal cells, which makes the skin smooth, sebum also impregnates the epidermis, reducing water loss. It is a medium for symbiotic bacteria, on the other hand, it gives a low pH and reduces the humidity of the epidermis surface, limiting the growth of bacteria.

Functions of the mammary glands. Of course, the primary function of the mammary glands is to produce milk. In case of humans, an extra function was created, related to partner selection: a very unusual gland development in the female sex (with an overgrown adipose tissue) only serves as attractor for the male.

7. Healing and regeneration of the skin

The skin is a barrier that protects the body against the environment, so any defects in the skin continuity must be quickly and effectively repaired. Wound healing can occur through tissue regeneration or tissue repair. In the case of shallow cavities, abrasions of the outer layers of the epidermis, regeneration takes place, i.e. the process of multiplication of the basal layer cells and pushing them into more and more outer layers, in the same way as in the case of normal epidermal growth. If the reproductive cells of the basal layer have been destroyed, a multi-stage scar repair, a kind of temporary structure of connective tissue, is required. In this case, there are two options: if there are no complications, the wound healing is characterised by rapid growth, if the wound is extensive or contaminated, it heals by granulation.

Healing includes the phases of hemostasis, inflammation, proliferation, and remodeling. These phases will only be outlined, without being discussed in detail.

The hemostatic phase is the blood loss stopping by the formation of a clot. Clotting starts when blood comes into contact with collagen. The process is initiated by platelets, binding to collagen thanks to glycoprotein Ia/IIa receptors, specific to collagen. Both the platelets and epithelial cells of the vascular endothelium secrete von Willebrand coagulation factor which additionally stabilizes the adhesion of platelets to collagen. The platelets secrete inflammatory mediators such as serotonin, thromboxane, ADP, and a platelet activating factor. A plate plug is formed when they stick together. Subsequent processes lead to the transition of prothrombin to thrombin, which causes the soluble plasma protein – fibrinogen to change into insoluble fibrin which precipitates on the platelet plug. At the same time, the inflammatory process occurs. Under the influence of chemotactic factors (fibronectin, kinins, growth factors), new neutrophils, lymphocytes and monocytes continue to flow to this place, developing an inflammatory reaction. After reaching the place, the monocytes differentiate into macrophages, which, apart from phagocytosis, perform other functions: under hypoxic conditions in damaged tissues, they release factors that induce regeneration, including cytokines and growth factors, stimulating angiogenesis (formation of new blood vessels), regeneration of connective tissue, and also epithelialization (regeneration of the epithelium).

In the proliferation phase, there is a rapid multiplication of cells, combined with the synthesis of the intercellular substance of the connective tissue. Granulation leads to the formation of granulation tissue, i.e. a young form of connective tissue. Within two to five days of injury, fibroblasts begin to creep into the healing site under the influence of, among others, PDGF, TGF – β and fibronectin. They use the fibrin fibres of the clot to travel, then the newly synthesized collagen fibers. Then, the fibroblasts multiply and start synthesizing the intercellular substance. The area of the defect is filled with granulation tissue – freshly formed young connective tissue, strongly supplied with blood by the simultaneously emerging blood vessels. The collagen formed at this stage is type III collagen. As connective tissue regenerates, neoangiogenesis occurs, i.e. the construction of new blood vessels. The endothelial cells of the surrounding tissues are activated and released by protease, therefore they can migrate under the influence of chemotactic factors assisted by low oxygen levels. They arrange themselves in the right places and create a new basement membrane in the endothelium of a new blood vessel. At the same time, epithelialization takes place, that is, the cells of the basal layer of the epithelium (epidermis) fill the damaged area in order to synthesize there a new membrane with the basis and start proliferation. The cells change shape and produce a kind of pseudopodia thanks to actin fibres. If the wound is not too extensive, the source of cells are the margins of the wound and deep clusters of epithelial germ cells, e.g. matrix of hair roots or skin glands. The described processes can only take place on the living tissue, in a humid environment. Therefore, the healing wound should not overdry. After migration, the basement membrane is restored, its connections and intercellular junctions are restored, and the new basal layer begins to proliferate and produce subsequent layers of the epidermis. If a scar remains from the site of the damage, the glands and hair will not be rebuilt there.

The last and longest healing process is remodeling. The initial collagen synthesis during healing was chaotic in order to restore the skin barrier as soon as possible. The remodeling is very precise, new type I fibers are formed according to the lines of forces and tensions in the skin. The remodeling of the fibers begins within a few weeks of an injury, and it may take years. At the same time, there is a reduction in the number of blood vessels, which also do not have to actively supply the already built tissue. Healing disorders can lead to e.g. keloids, hypertrophic scars, varicose ulcers.

Examples of issues:

1. The function of the skin in the water and electrolyte balance.
2. The role of the skin pigment.
3. Skin receptors. The role of the skin in protection against microorganisms.
4. Hormonal regulation of the skin functions.
5. The role of the skin in protecting against water loss.
6. Functions of the sebaceous glands.
7. Functions of the sweat glands.
8. Functions of hair.
9. Protective functions of the skin.
10. Skin's participation in the hormonal balance.
11. Healing and regeneration of the skin.

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