

Assessment of the Embryological Origin, Anatomical and Histological Structure of the Skin

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Abstract

The skin is at the interface between the organism and the environment, realizing the element of unity that the totality of the organs and systems in the human body has. Through its structure and position on the human body, the skin has a main role in the economy of the whole organism; it also has an aesthetic role. The objective of this study is to assess the embryological origin, anatomical and histological structure of the skin. The skin consists of the epidermis, which is of ectodermal origin, and the dermis, which is of mesodermal origin. The most important functions of the skin are the protection, thermoregulation, control of fluid loss, immunity, and sensory perception. The source of the cutaneous vessels comes directly from arterial sources otherwise, as terminal branches of muscular vessels. Various specialized anatomical structures are placed in the skin to receive different stimuli: free nerve endings, Merkel cells, Meissner corpuscles, Pacinian corpuscles, Krause bulbs, Ruffini corpuscles, proprioceptors for cold and heat. Various post-lesion changes in the skin can affect daily activities in the sense of alienation and isolation from significant people, and in some situations, can lead to job loss, neurotic disorders, and negative social consequences.

Keywords: Skin, Skin anatomy, Embryological origin, Histological structure

INTRODUCTION

Since the beginning of civilization, physical appearance has been an important criterion for defining the place, role, and social connection of each person in front of others. The physical aspect had a major contribution in determining the social status, respectively the ascent or descent on the social scale. Nowadays, a pleasant appearance ensures success in all social plans, with a predilection for women, but with the modernization of societies and gender equality policies, the physical appearance of men tends to increase in importance [1-3].

In high-paying jobs that do not have a high degree of complexity, such as modeling, advertising, television, and social media careers, physical appearance is used almost as the sole criterion for inclusion. Therefore, the characteristics of the skin have a major importance in beauty. The presence of scars that affect the area of importance in the expression of non-verbal language or those that modify the natural symmetry of the face lead to aesthetic damage, and the negative consequences of aesthetic damage are mainly felt in the family and professional sphere, without losing sight of the fact that any person suffers from awareness of unsightly wounds or scars [4-6].

The objective of this study is to assess the embryological origin, anatomical and histological structure of the skin.

Skin: Definition and Embryonic Origin

Human skin covers the entire exterior of the body. One of the most important functions of the skin is the protection offered to the body when interacting with the external environment such as toxins, viruses, bacteria, ultrasound radiation, or extreme temperatures. In addition, the skin includes several functions such as thermoregulation through sweating, control of fluid loss, role in immunity, and sensory perception. The integument represents approximately 16% of body weight, and in adults, it has a surface between 1.2 - 2.3 m² [7, 8].

The anatomical structure consists of three layers: epidermis (ectodermal origin) and dermis (mesodermal origin). Beneath the dermis is the subcutaneous tissue, or hypodermis, whose structure differs from that of the integument. The hypodermis consists of loose connective tissue, a hypodermic adipose

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panicle that is rich in fat cells, and a macroscopic counterpart of the superficial fascia ensuring the skin's loose adhesion to the underlying layers [9].

The epidermis, as an embryonic origin, comes, like the central nervous system, from the ectoderm. It consists of a keratinized stratified squamous epithelium and other three cell types that are less numerous: melanocytes, Merkel cells, and Langerhans cells. Melanocytes are responsible for skin pigmentation, and as an origin, they come from neural crests; Langerhans cells are cells involved in the processing of antigens and originate in the bone marrow; sensitive Merkel cells are responsible for sensing pressure and also originate in neural crests [10, 11].

As a rule, one type of skin is thick integument: smooth, glabrous, or hairless skin, and the other type is thin, hairy integument [12].

The epidermis is made up of five layers of keratin-producing cells: the basal or germinal layer, the spinous layer, the stratum granulosum, the stratum lucidum, and the stratum corneum.

The basal layer of the epidermis presents a single row of basophilic cylindrical or cuboid cells, located on the basal membrane of the epidermis, at the level of the dermo-epidermal junction, they present desmosomes that join the cells together, and hemidesmosomes fix the cells to the basal membrane of the epithelium. The basal layer consists of stem cells and exhibits intense mitotic activity, being responsible for the continuous renewal of the spinous layer. Human epidermal cells renew at an interval between 15 and 30 days, depending on age, and topography [13, 14].

The spinous layer consists of cuboid cells, with a central nucleus and fine cytoplasmic extensions that contain bundles of keratin filaments, called tonofilaments, and in the apical portion, they present desmosomes, with a role in maintaining intercellular cohesion and resistance to abrasion. For example, plants contain several keratin filaments and desmosomes. At this level, only the malpighian layer contains stem cells [15].

The third layer of the epidermis is the granular layer; it shows 3-5 rows of flattened polygonal cells with cytoplasmic content of keratohyalin granules. These cells do not have their own membranes. The granular content layer acts as a barrier that prevents the penetration of foreign bodies into the granular layer, therefore determining the impermeability of the integument. The stratum lucidum is translucent, and thin, and shows flattened eosinophilic epidermal cells. The last layer of the epidermis, the stratum corneum, has 15-20 rows of keratinized, flattened, anucleated cells that contain keratin. Corneal cells are continuously removed by desquamation at the surface of the stratum corneum [16, 17].

The dermis is the second layer of the integument and derives mainly from the mesoderm. It consists of collagen and elastic fibers, fibroblasts, and blood vessels.

Embryological differentiation begins throughout the fourth week of embryonic life. It is manifested by the differentiation and proliferation of the ectoderm and mesoderm. During this period, specialized structures appear such as hair, nails, sweat and sebaceous glands, apocrine and mammary glands, and teeth [18].

Studies have shown that hair, hair follicles, and teeth originate from both, the epidermis and dermis, whereas nails originate only from the epidermis. At birth, the skin is present as a definitive stage of the multilayered epidermis. This, throughout life, undergoes a continuous process of modification, in which the old layers are replaced by new ones. The skin thickness variate depending on gender, location, and age. The dermis thickness is given by the thickness of the integument because the epidermis is normally constant throughout its lifetime. The greatest thickness of the integument is approximately 1.5 mm, located in the palm and plant, and the thickness is 0.05 mm at the eyelids level [19].

Skin Structure

The first layer of the skin is the epidermis, which is in contact with the environment. The epidermis does not contain blood vessels and, therefore, is completely dependent on nutrition on the dermis, which supplies it with nutrients through the process of diffusion. This is a stratified squamous epithelium, formed by keratinocytes in different stages of differentiation, the least differentiated are those in the deep layer, and the best differentiated are in the superficial layer. The substructure of the epidermis consists of 4 layers starting from the depth with the germinal layer, the spinous layer, the granular layer, and the corneous layer.

Keratinocyte

The germ layer or basal layer is located immediately above the dermo-epidermal junction. It consists of a single layer of keratinocytes and is connected to the basement membrane through hemidesmosomes. After dividing and differentiating keratinocytes, they move from the deep layer to the more peripheral layers. In the stratum corneum, the keratinocytes are completely differentiated and lose the nucleus, which is subsequently sloughed off in the skin renewal process [20].

Melanocyte

It is the cell whose main function is the production of pigment and melanin (it absorbs ultraviolet radiation, produced by the sun, with a mutagenic effect). Melanin accumulates in organelles called melanosomes, which are embedded in the dendrites that anchor the melanocyte to the surrounding keratinocyte. There is a process of transfer of melanosomes by phagocytosis to keratinocytes where they are stored in the form of granules. Melanocytes are developed in the epidermal

basal layer, moreover, in the retina, hair follicles, leptomeninges, etc. The ratio between melanocytes and keratinocytes is 1:4, in zones exposed to the sun, and in those less exposed to the sun, the ratio is 1:30. The absolute number of melanosomes is equal in both sexes and different races [21, 22].

The difference in pigmentation between individuals is due to the different sizes of the melanosomes. Exposure to the sun causes the production of melanocyte-stimulating hormone (MSH), cortico-stimulating hormone, estrogen, and progesterone, which together stimulate melanin production. Melanin is synthesized in melanocytes, and its storage is at the level of epithelial cells that contain a greater amount of melanin compared to melanocytes [23]. Skin pigmentation is conditioned by 3 factors:

- Melanin synthesis rate at the level of melanocytes;
- Transfer of melanin granules in keratinocytes;
- Storage of granules at the level of keratinocytes.

Melanocytes secrete a dark brown pigment called eumelanin, a pigment specific to red hair, and pheomelanin, which contains a large number of cysteine molecules. With advancing age, a decrease in the number of melanocytes because it was observed that melanocytes cannot reproduce [24].

Langerhans Cells

These cells originate from the bone marrow. The Langerhans cells (LCs) are detected in the basal layer, spinous and granular layer. They perform as antigen-presenting cells, having a role in the body's immunity. They can phagocytose foreign antigens, process them into short-chain peptide segments, bind them to the major histocompatibility complex, and then present them to lymphocytes for immune system activation [25].

Merkel Cells

They come from the neural crest and are distributed on the palmar side of the fingers, in the nail bed, in the genital region, and other zones of the skin. The Merkel cells are discerned in the sensation of fine touch. It is assumed that they have the role of mechanoreceptors, but some studies have shown the possibility of their belonging to the diffuse neuroendocrine system. The dermis is a structure consisting of 2 layers, the external or the papillary dermis, and the other, deep, is the reticulated dermis. It supports the epidermis and attaches it to the hypodermis. The papillary dermis is thin, it is composed of loose connective tissue, which contains elastic and reticular fibers, capillaries, and collagen. The reticular dermis is the thicker layer and consists of dense connective tissue, which contains larger blood vessels, and interspersed elastic and collagen fibers, ordered in parallel layers to the surface. Furthermore, this layer comprises lymphatics, fibroblasts, nerve endings, mast cells, and epidermal appendages. These components of the dermis are surrounded by a gelatinous fundamental substance containing

glycoproteins, mucopolysaccharides, and chondroitin sulfate [26].

The profound area of the dermis is unequal and the margins of the subcutaneous layer of adipose panicles act as a shock absorber for the skin.

Fibroblasts form the majority of cells in the dermis. The fibroblast produces elastic fibers and procollagen. Procollagen is divided by proteolytic enzymes into collagen, which is then combined and becomes a reticulated network. This tight collagen network provides the strength and resistance needed to withstand mechanical force. Collagen represents 70% of the weight of the dermis and is made up of 85% type I collagen and 15% type III collagen. Elastic fibers make up less than 1% of the dermis' weight, but they have an important functional role, resisting deformation forces and restoring the skin's original shape [27].

Derma-Epidermal Junction

This is a wavy basement membrane that connects the epidermis to the dermis. It consists of two laminae: lucida and densa. Lamina lucida is thin and lies straight on the basal layer of the basal keratinocyte layer. Lamina densa is thicker, it is in contact with the underlying dermis. The dermal papillae hold capillaries and lymphatics, arranged perpendicular to the skin area. These digitiform projections are bordered by related projections in the epidermis. These asymmetrical junctions increase the exchange area for nutrients, oxygen, and catabolism products, through the dermis and the avascular epidermis [28].

Accessory Glands of the Epidermis

Epidermic appendages are intradermal structures, covered with epithelial cells. These appendages have a great potential for differentiation and division, important in the formation of epithelial cells that can fulfill the role of re-epithelialization in case of removal of the overlying or destroyed epidermis (superficial burns, excoriations, or skin graft). Epidermal appendages comprise sebaceous and sweat glands, apocrine and mammary glands, and hair follicles. These are frequently found in the depth of the dermis and can even be placed on the fat in the hypodermic layer, this placement consists of the remarkable capacity of re-epithelialization even in deep skin lesions. Holocrine glands or sebaceous glands are encountered on the whole side of the body, excluding the palms, soles, and the dorsal side of the foot. The elevated concentration is found on the scalp and face, where it is the most common place of acne origin. The common function of the sebaceous gland is to secrete sebum, which is a complex of oils, which includes triglycerides, fatty acid excretion products - ceruminous esters, cholesterol ester, squalene, and cholesterol. Sebum greases the skin to protect the skin against abrasion and makes the skin impermeable to moisture.

Sweat glands or eccrine glands are located on the entire area of the body, except the red lip, external auditory canal, labia

minora, nail bed, the glans penis, and the inner face of the foreskin. The most condensed areas are in the palms, soles, and armpits. Every gland is composed of a spiral, the secretory intradermal portion that connects to the epidermis through a straight, distal duct. The common function of sweat glands is to secrete sweat, which cools the body by evaporation [29, 30].

The hypothalamus contains the thermoregulatory center that controls the sweat glands' activity through a sympathetic nerve. The production of the sweat glands is set when the body temperature exceeds the normal temperature [31].

Apocrine and Mammary Glands

Apocrine glands are comparable in structure, but not identical to eccrine glands. They are found in the armpits, in the anogenital region and modified glands are found in the external auditory canal (ceruminous glands), and eyelids.

Moll's glands and breasts (mammary glands).

They secrete odor and do not function before puberty, which probably means that they have a vestigial function. The mammary gland is considered to be a highly specialized apocrine gland [32].

Hair follicles are anatomic structures formed by both, the epidermis and dermis. On the body, these follicles are located on the entire surface, excluding the palms, soles, clitoris, labia minora, glans, portions of the fingers and toes, and mucocutaneous junction. The sebaceous glands regularly open in these follicles, rather directly on the skin surface, the whole complex being called pilosebaceous unit.

The hair bulb is the base of the hair follicle, placed profound in the dermis, however at the level of the face it can be placed on the subcutaneous fat, a particularly important aspect in the remarkable ability of re-epithelialization, even in very deep wounds. Hair growth has two cyclical phases, the anagen phase represents the growth, and the second, the telogen, represents the latent phase. The transition into these two phases is termed the catagen phase. The anatomical localization and period of the anagen phase are correlated to the length of the hair produced [33].

Subcutaneous Tissue

The subcutaneous tissue or hypodermis presents a connective structure that provides the loose resistance of the skin to the underlying anatomical formations. It contains adipocytes that have different sizes, depending on the nutritional status of the person.

Skin Phototype

The quantity of melanin pigment determines the individual skin color. The pigment in the skin can be determined genetically otherwise, it can be received throughout varied disorders. The pregnancy represents one hormonal factor that changes the quantity of melanin secretion and its distribution.

Among the factors that condition skin color, we note the content of melanin and carotene, the number of blood vessels in the structure of the dermis, but also the color of the blood that circulates through them [34].

The Fitzpatrick scale is used to classify the complexity of the skin's response to exposure to ultraviolet rays. This scale is based on individual history of sunburn and tanning and is utilized for clinical assessment of the pigmentation of the face, prior to skin resurfacing methods, for prognosis and adverse effects. The scale divides the skin into six types, the first corresponds to the color of white or freckled skin, having characteristic sunburns always produced by exposure to ultraviolet rays and never tanning [35-37].

Vascularization of the Skin

Cutaneous vessels originate from the underlying vessels. Each vascular source provides a three-dimensional area of skin, from bone to skin, in a formation called angioma. Adjacent angiosomes have vascular connections between them, through small- or normal-sized vessels. The source of the cutaneous vessels comes directly from arterial sources (perforating septo-cutaneous or fasciculo-cutaneous) otherwise, as terminal branches of muscular vessels (perforating musculo-cutaneous). In the course of their route to the integument, cutaneous vessels cross through or past the connective tissue network and give branches to each tissue they come into close contact with (muscle, fascia, nerves, bone, and fat). Blood vessels come from the deep fascia, and enter surrounding the intramuscular and intermuscular septum, near the tendons. These vessels go into the skin to organize the dermal and subdermal plexus [36].

The dermis holds both, superficial and profound plexuses placed horizontally. These plexuses are interconnected by communicating vessels oriented perpendicular to the surface of the skin. Cutaneous vessels anastomose with other cutaneous vessels to create a continuous network in the skin. The lymphatic vessels are parallel to the blood vessels and have an important role in the preservation of plasma and proteins, bacteria, and antigenic substances. The blind ends of the lymphatic capillaries are formed at the level of the interstitial space of the dermal papillae. These nonvalvular, superficial dermal vessels drain into the dermal and subdermal valvular plexuses and fuse to form lymphatic channels that flow through numerous lymph nodes, which filter the lymph on its way to the venous circulation near the junction of the subclavian vein and the internal jugular vein [37].

Skin Innervation

Sensory perception is of critical importance in avoiding pressure, traumatic or mechanical forces, and extreme temperatures. Various specialized anatomical structures are placed in the skin to receive different stimuli. Merkel cells (located in the epidermis, in the skin ridges, and sheaths of hair follicles) and Meissner corpuscles (located in the papillae

of the dermis) detect light touch. They are placed in the dermal papillae and have a maximum concentration at the level of the fingertips [38].

Furthermore, the Pacinian corpuscles are located in the deep dermis, moreover, in the hypodermis, their function is to detect pressure. According to Sherrington, there are two forms of tactile sensitivity: protopathic and epicritic. Protopathic is an undifferentiated, coarse, diffuse tactile sensitivity, and epicritic represents fine, discriminative tactile sensitivity. The pain is passed through free nerve endings, placed in the epidermis, in the basal layer. If a certain intensity of thermal or tactile sensation is exceeded, it will be perceived as pain.

Krause bulbs recognize cold and Ruffini corpuscles detect heat. Proprioceptors for cold and heat are placed in the external dermis. The cutaneous nerves accompany the path of blood vessels.

The area innervated by one spinal nerve or one part of the spinal cord is called a dermatome. Adjacent dermatomes can overlap, this is crucial when conducting anesthesia at the level of nerve blocks [39, 40].

CONCLUSION

The skin is at the interface between the organism and the environment, realizing the element of unity that the totality of the organs and systems in the human body has. Through its structure and position on the human body, the skin has a main role in the economy of the whole organism; it also has an aesthetic role. Various post-lesion changes in the skin can affect daily activities in the sense of alienation and isolation from significant people, and in some situations, can lead to job loss, neurotic disorders, and negative social consequences.

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REFERENCES

1. Khavkin J, Ellis DA. Aging skin: Histology, physiology, and pathology. *Facial Plast Surg Clin North Am.* 2011;19(2):229-34. doi:10.1016/j.fsc.2011.04.003
2. Căiță GA, Maghiar T, Bodog FD, Maghiar L, Voită-Mekereş F, Lascu CF. A review of social factors affecting women's tendency to cosmetic surgery. *Pharmacophore.* 2023;14(1):111-5. doi:10.51847/GOEDyJpSvD
3. Mekereş F, Voită GF, Mekereş GM, Bodog FD. Psychosocial impact of scars in evaluation of aesthetic prejudice. *Rom J Leg Med.* 2017;25:435-8.
4. Mekeres GM, Voită-Mekereş F, Tudoran C, Buhaş CL, Tudoran M, Racoviță M, et al. Predictors for estimating scars' internalization in victims with post-traumatic scars versus patients with postsurgical scars. *Healthcare (Basel).* 2022;10(3):550. doi:10.3390/healthcare10030550
5. Voită-Mekereş F, Buhaş CL, Mekeres GM, Tudoran C, Racoviță M, Faur CI, et al. Mekeres' psychosocial internalization scale: A scale for

- the evaluation of aesthetic prejudice in victims of accidents and violence. *Healthcare (Basel).* 2021;9(11):1440.
6. Paşcalău AV, Cheregi CD, Mureşan MŞ, Şandor MI, Huniadi CA, Nikin Z, et al. CD4+ CD25+ regulatory T-cells role in tumor microenvironment of the squamous cell carcinoma. *Rom J Morphol Embryol.* 2021;62(1):249-53.
7. Tienda-Vázquez MA, Hanel JM, Márquez-Arteaga EM, Salgado-Álvarez AP, Scheckhuber CQ, Alanis-Gómez JR, et al. Exosomes: A promising strategy for repair, regeneration and treatment of skin disorders. *Cells.* 2023;12(12):1625. doi:10.3390/cells12121625
8. Zouboulis CC, Makrantonaki E. Clinical and laboratory skin biomarkers of organ-specific diseases. *Mech Ageing Dev.* 2019;177:144-9. doi:10.1016/j.mad.2018.08.003
9. Visscher MO, Carr AN, Narendran V. Epidermal immunity and function: Origin in neonatal skin. *Front Mol Biosci.* 2022;9:894496. doi:10.3389/fmolb.2022.894496
10. Lee J, Rabbani CC, Gao H, Steinhart MR, Woodruff BM, Pflum ZE, et al. Hair-bearing human skin generated entirely from pluripotent stem cells. *Nature.* 2020;582(7812):399-404. doi:10.1038/s41586-020-2352-3
11. Tudoran C, Tudoran M, Abu-Awwad A, Cut TG, Voită-Mekereş F. Spontaneous hematomas and deep vein thrombosis during the recovery from a SARS-CoV-2 infection: Case report and literature review. *Medicina (Kaunas).* 2022;58(2):230. doi:10.3390/medicina58020230
12. Mekeres GM, Buhaş CL, Csep AN, Beişanu C, Andreescu G, Marian P, et al. The importance of psychometric and physical scales for the evaluation of the consequences of scars-A literature review. *Clin Pract.* 2023;13(2):372-83. doi:10.3390/clinpract13020034
13. Goleva E, Berdyshev E, Leung DY. Epithelial barrier repair and prevention of allergy. *J Clin Invest.* 2019;129(4):1463-74. doi:10.1172/JCI124608
14. Mekeres GM, Buhaş CL, Bulzan M, Marian P, Hozan CT. Objective criteria in evaluating the consequences of the posttraumatic scars. *Pharmacophore.* 2022;13(1):56-61.
15. Cavalu S, Simon V, Albon C, Hozan C. Bioactivity evaluation of new silver doped bone cement for prosthetic surgery. *J Optoelectron Adv Mater.* 2007;9(3):690.
16. Wertz P. Epidermal lamellar granules. *Skin Pharmacol Physiol.* 2018;31(5):262-8. doi:10.1159/000491757
17. Nicoara ND, Varga D, Voita-Mekeres F, Galea-Holhos L, Andreescu G, Costas L. Study of basic emotions in the general population using the Likert scale. *Pharmacophore.* 2023;14(4):14-21. doi:10.51847/tjyOah1VwM
18. Voită-Mekereş F, Voită GF, Pogan MD, Delcea C, Manole F, Mekeres GM, et al. Clinical considerations of dental longevity from the lateral area. *Pharmacophore.* 2023;14(3):100-6.
19. Alibardi L. General aspects on skin development in vertebrates with emphasis on sauropsids epidermis. *Dev Biol.* 2023;501:60-73. doi:10.1016/j.ydbio.2023.05.007
20. Suman S, Domingues A, Ratajczak J, Ratajczak MZ. Potential clinical applications of stem cells in regenerative medicine. *Adv Exp Med Biol.* 2019;1201:1-22. doi:10.1007/978-3-030-31206-01
21. Chen J, Li S, Li C. Mechanisms of melanocyte death in vitiligo. *Med Res Rev.* 2021;41(2):1138-66. doi:10.1002/med.21754
22. Davidescu L, Chanez P, Ursol G, Korzh O, Deshmukh V, Kuryk L, et al. Late breaking abstract – masitinib in severe asthma: Results from a randomized, phase 3 trial. *Eur Respir J.* 2020;56(64):4612.
23. Agar N, Young AR. Melanogenesis: A photoprotective response to DNA damage? *Mutat Res.* 2005;571(1-2):121-32.
24. Laiho L, Murray JF. The multifaceted melanocortin receptors. *Endocrinology.* 2022;163(7):bqac083. doi:10.1210/endo/bqac083
25. Rajesh A, Wise L, Hibma M. The role of Langerhans cells in pathologies of the skin. *Immunol Cell Biol.* 2019;97(8):700-13. doi:10.1111/imcb.12253
26. Lee J, Rabbani CC, Gao H, Steinhart MR, Woodruff BM, Pflum ZE, et al. Hair-bearing human skin generated entirely from pluripotent stem cells. *Nature.* 2020;582(7812):399-404. doi:10.1038/s41586-020-2352-3
27. Shigematsu T, Koiwa F, Isaka Y, Fukagawa M, Hagita K, Watanabe YS, et al. Efficacy and safety of upacicalcet in hemodialysis patients with secondary hyperparathyroidism: A randomized placebo-

- controlled trial. *Clin J Am Soc Nephrol.* 2023;18(10):1300-9. doi:10.2215/CJN.0000000000000253
28. El Genedy-Kalyoncu M, Richter C, Surber C, Blume-Peytavi U, Kottner J. The effect of a basic skin care product on the structural strength of the dermo-epidermal junction: An exploratory, randomised, controlled split-body trial. *Int Wound J.* 2022;19(2):426-35. doi:10.1111/iwj.13643
 29. Lacouture ME, Patel AB, Rosenberg JE, O'Donnell PH. Management of dermatologic events associated with the nectin-4-directed antibody-drug conjugate enfortumab vedotin. *Oncologist.* 2022;27(3):e223-32. doi:10.1093/oncolo/oyac001
 30. Mekereș GM, Buhaș CL, Tudoran C, Csep AN, Tudoran M, Manole F, et al. The practical utility of psychometric scales for the assessment of the impact of posttraumatic scars on mental health. *Front Public Health.* 2023;11:1103714. doi:10.3389/fpubh.2023.1103714
 31. Tan CL, Knight ZA. Regulation of body temperature by the nervous system. *Neuron.* 2018;98(1):31-48. doi:10.1016/j.neuron.2018.02.022
 32. Shah A, Tsianou Z, Suchak R, Mann J. Apocrine chromhidrosis. *Am J Dermatopathol.* 2020;42(10):e147-8. doi:10.1097/DAD.0000000000001712
 33. Usmani AS. Hair follicle bulb region: A potential nidus for the formation of osteoma cutis. *Cutis.* 2021;107(1):E31-4. doi:10.12788/cutis.0180
 34. Passeron T, Lim HW, Goh CL, Kang HY, Ly F, Morita A, et al. Photoprotection according to skin phototype and dermatoses: Practical recommendations from an expert panel. *J Eur Acad Dermatol Venereol.* 2021;35(7):1460-9. doi:10.1111/jdv.17242
 35. Shope CN, Andrews LA, Neimy H, Linkous CL, Khamdan F, Lee LW. Characterizing skin cancer in transplant recipients by fitzpatrick skin phototype. *Dermatol Ther (Heidelb).* 2023;13(1):147-54. doi:10.1007/s13555-022-00858-z
 36. Coroi MC, Bakraoui A, Sala C, Țica O, Țica OA, Jurcă MC, et al. Choroidal melanoma, unfavorable prognostic factors. Case report and review of literature. *Roman J Morphol Embryol.* 2019;60(2):673-8.
 37. Holhoș LB, Coroi MC, Lazăr L. Observations on refractive status and risk factors for visual impairment in children with disabilities. *Medicina.* 2021;57(5):403.
 38. Lee HJ, Hong YJ, Kim M. Angiogenesis in chronic inflammatory skin disorders. *Int J Mol Sci.* 2021;22(21):12035. doi:10.3390/ijms222112035
 39. Ogawa R. Keloid and hypertrophic scars are the result of chronic inflammation in the reticular dermis. *Int J Mol Sci.* 2017;18(3):606. doi:10.3390/ijms18030606
 40. Laverdet B, Danigo A, Girard D, Magy L, Demiot C, Desmoulière A. Skin innervation: Important roles during normal and pathological cutaneous repair. *Histol Histopathol.* 2015;30(8):875-92. doi:10.14670/HH-11-610