

# Epidemiology of dermatological diseases - aging, metabolic diseases and beyond

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## Abstract

More than forty different diseases are associated with dermato-pathological problems. The skin is the largest organ of the body - as any organ, its constitutive elements are, under physiological conditions, controlled by signals arising from the central, peripheral and autonomous nervous systems. Consequently, a plethora of problems affecting central nervous system (CNS) and non-CNS-mediated functions may lead secondarily to skin problems. As of now, the industry has generally failed to provide safe and potent drugs and therapeutics capable of fulfilling each of these specific unmet medical needs - most skin care products don't even meet safety standards and requirements, as imposed by regulatory authorities for approval and marketing of pharmaceutical products (i.e., small molecule therapeutics or biologics). Thus, next-generation drugs and therapeutics for skin diseases will probably be increasingly acting upon central and peripheral mechanisms for superior efficacy which, in turn, shall force regulatory authorities to impose stricter regulations for approval and marketing of dermatological products.

## Introduction

The skin is the largest organ of the body and the first line of defense against external pathogens. Dysfunctional skin is in fact associated with several debilitating pathological conditions such as xerosis and atopic dermatitis (see complete list below) [1] (Table 1).

The International League of Dermatological Societies (ILDS) has identified the consequences of skin aging as one of the most important grand challenges in global skin health [2]. As we get older, the skin undergoes significant changes - many of which may be attributed to systemic, metabolic, and lifestyle changes. According to the World Health Organization, the number of people aged 65 or older is projected to grow from 524 million (2010) to nearly 1.5 billion in 2050 (who.int/ageing). However, the incidence of those who will be dealing with skin problems remains unknown. Other underlying conditions or diseases are also known to alter skin health. Environmental problems such as pollution negatively affect skin health (see complete list below (Table 2)). Diabetes is also a leading cause skin problem. Skin disorders, usually neglected and frequently underdiagnosed among diabetic patients, are common complications and encounter a broad spectrum of disorders in both type 1 and type 2 diabetes mellitus - e.g. cutaneous infection, dry skin, pruritus. Skin disorders are highly associated with increased risk of important outcomes, such as skin lesions, ulcerations

and diabetic foot, which can lead to major complications and revolve around multifactorial factors besides hyperglycemia and advanced glycation end products [3].

Physicians are aware that climatic conditions negatively affect the skin. Low humidity and low temperatures lead to a general decrease in skin barrier function and increased susceptible towards mechanical stress. Since pro-inflammatory cytokines and cortisol are released by keratinocytes, and the number of dermal mast cells increases, the skin also becomes more reactive towards skin irritants and allergens [4]. Regarding prevalence, skin diseases may be considered one of the greatest problems of all time. For instance, according to data from NIAMS (National Institute of Arthritis and Musculoskeletal and Skin Disease), more than 5.5 million people in the U.S. suffer of psoriasis, 17 million live with acne and 5 million with vitiligo. According to the British Skin Foundation, 8 million people in the U.K. are currently living with one of the skin diseases. Several

Table 1. Pathological conditions of dysfunctional skin.

xerosis	sebaceous cyst	vitiligo
atopic dermatitis	seborrheic keratosis	lupus
skin cancer	pilonidal sinus	eczema
hemangioma	ichthyosis vulgaris	impetigo, abscess
cold sore	psoriasis	decubitus ulcer
cutaneous candidiasis	rosacea	herpes
carbuncle	hives	fungal nail infection
acne vulgaris	hypohidrosis	pruritus
alopecia areata	fungal skin diseases	non-melanoma skin cancer
decubitus ulcer	cellulitis	psoriasis
urticaria, scabies	molluscum contagiosum	sun burn

Table 2. Factors affecting the skin disorders.

andropause-aging	brain swelling	pressure
menopause-aging	glaucoma	friction
diabetes	obesity	mobility problems
environment	malnutrition	paralysis
climatic conditions	epilepsy	vascular problems
lifestyle	pharmaceutical products	arthritis
epigenetics	depression	Alzheimer's disease-aging
viral infection	inflammatory diseases	dementia
drug abuse	cardiovascular diseases	herpes
cancer	infectious diseases	-

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cellular mechanisms, either CNS or non-CNS related may underlie skin diseases and pathological conditions. Dysregulation of skin receptors (nociceptor, mechanoreceptor, etc.) may constitute one of the problems. They normally send directly or indirectly to the central nervous system, inputs involved in assessing hot/cold, pressure/touch, pain, vibration, or chemicals as well as vasoconstriction, vasodilatation, body temperature regulation, barrier function, secretion, growth, differentiation, cell nutrition, nerve growth, inflammatory and immune responses, apoptosis, proliferation, and wound healing [1]. Water transport problems may also underlie skin, and particularly dry skin problems. Water content levels depend indeed on water transport from inner layers, including from blood vessels, seeks bringing in water towards the dermis and, hence, the epidermis. Once SC layer is reached, water is eventually being lost to evaporation. Consequently, to decrease water content losses, it is imperative to limit evaporation and sweating in some conditions. Aquaporin channels, supported by water-binding molecules such as glycerol, expressed on vascular endothelial cells, facilitate water exchange and transport between blood and dermis [5]. Blood volumes, circulating flow levels and regional distribution are directly affecting water transport levels [6]. Actions upon these systems critically depend upon a complex variety of neural mechanisms – i.e., hypothalamic-pituitary-adrenal axis (e.g., arteriovenous anastomoses) raphe nucleus, medulla oblongata, preoptic area, hypothalamus, pons and periaqueductal gray matter [7-11]. Recording skin sympathetic nerve activity has revealed that a large fraction of the sympathetic activity during heat stress is essentially sudomotor in nature through acetylcholine release that binds to muscarinic receptors. Other neural systems may be involved (e.g.,  $\alpha$ - or  $\beta$ -adrenergic, vasoactive intestinal polypeptide, calcitonin gene-related peptide) [12-14]. The human skin and its sebaceous glands express a plethora of neuropeptidergic receptors – e.g., corticotropin-releasing hormone, transient receptor potential vanilloid-1, melanocortins,  $\beta$ -endorphin, vasoactive intestinal polypeptide, neuropeptide Y, substance P, and calcitonin gene-related peptide which may become dysfunctional or with altered expression levels [15,16].

Other main pathological conditions known for altering skin cells and functions include brain swelling, glaucoma, epilepsy, obesity, malnutrition and cancer [17-22]. Unfortunately, most related mechanisms are, as of now, only considered as future cellular targets for next-generation CNS or non-CNS products against specific skin disease or dry skin problems. It will be pivotal for scientists to rapidly identify and develop potent therapies adapted to each condition for ensuring that skin and dry skin problems could, one day, be efficiently and safely treated.

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