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Basis for emergence of Seborrheic dermatitis

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Abstract

Introduction. Seborrheic dermatitis (SD) is commonly associated with presence of *Malassezia* fungi. As a part of microbiome *M. restricta, M. furfur, M. globosa* protects us from pathogenic bacteria and UV-light and can be found at any skin zone of our body, except palms and feet. Hyperproduction of sebum, inflammation, and itching as symptoms of SD also are caused by many diseases related with endocrine, neuro-, immune, and psychological disorders. It is impossible to unambiguously identify the cause of inflammation of the skin in areas of large accumulation of sebaceous glands. Therefore, current treatment of patients with seborrheic dermatitis requires a personalized and predictive approach including skin phenotype, somatic and mental comorbid disease.

Objective: to determine the factors that create the prerequisites for the development of dermatitis and overgrowth of Malassezia spp.

Materials and methods: Articles from Wiley online library, Cochrane library, Medline were analyzed**.**

Conclusions: SD should be considered as an early manifestation or visible symptom of somatic or mental illnesses. *Malassezia* colonization in sebaceous areas is an outcome, not a cause of SD.

Key words: *Malassezia spp.*, seborrheic dermatitis, sebaceous gland.

Передумови для виникнення себорейного дерматиту

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Реферат

Вступ. Себорейний дерматит (СД) часто асоціюють з присутністю на шкірі гибів роду *Malassezia*. Будучи частиною мікробіому *M. restricta, M. furfur, M. globosa* захищають від впливу УФ-випромінювання та патогенних бактерій та колонізують практично всі ділянки шкіри, крім долонь та стоп. Надмірна секреція шкірного сала, запалення та свербіж, які прийнято вважати основними симптомами СД, частіше за все спричинені нейро-, ендокринними, імунними та психічними розладами. Неможливо точно встановити причину запалення шкіри у ділянках з великою кількістю сальних залоз. Тому сучасне лікування пацієнтів з себорейним дерматитом повинно мати персоналізований та предиктивний підхід і враховувати фенотип шкіри, соматичні та психічні коморбідні розлади.

Метою дослідження було встановити фактори, які створюють передумови для виникнення себорейного дерматиту та надмірного росту *Malassezia spp.*

Матеріали та методи: аналіз оригінальних досліджень з бібліотек Wiley online library, Cochrane library, Medline.

Висновки. Себорейний дерматит варто розглядати як прояви маніфестації чи єдині видимі симптоми деяких соматичних та психічних захворювань. Колонізація запалених ділянок шкіри грибами *Malassezia spp.* є наслідком адаптації гриба до нових умов існування, а не причиною виникнення себорейного дерматита.

Introduction. It is believed that seborrheic dermatitis is often caused by fungi of the genus Malassezia. The main approach in SD therapy are drugs with antifungal activity: azoles, hydroxypyridones, allylamines, selenium and pyrithione of zinc, carbonic anhydrases[1]. But why corticosteroids[1], calcineurin inhibitors[2], cancer drugs[3], statins[4] help? In our opinion, Malassezia actively colonizes those areas of the skin where the environment is most favorable. And the basis for emergences of seborrheic dermatitis is the excessive production of sebum and required ph. Therefore, for good control of symptoms, it is necessary to treat the cause, not to eliminate the fungus.

Main reason of skin inflammation, desquamation and pruritus is based on idea of pathological activity of saprophytic fungi of the genus *Malassezia* (formerly known as *Pityrosporum*)[5] such as *Malassezia restrica*[6], *M. furfur*[7], *M. globosa*[8]. It is believed that *Malassezia spp.*:

- enhance the inflammatory response by inducing the synthesis of IL-1β, IL-ra to IL-1alpha, IL-8, but inhibit the synthesis of cytokines by keratinocytes,[9]
- synthesize metabolites that, acting on aryl-hydrocarbon receptors (Ah-receptors), impede the maturation of dendritic cells,[10]
- cause apoptosis of keratinocytes,[11]
- violate skin homeostasis,[12]
- are associated with Paget's disease[13] and carcinogenesis.[14]
- is capable of biofilm formation[15] and symbiosis with *Staphylococcus aureus*[16] and *Bacillus spp.*[17]

Malassezia have genes encoding secreted hydrolases (e.g., lipases, phospholipases, aspartyl proteases, and acid sphingomyelinases), but do not possess genes for fatty acid synthase [18]. Therefore, they are limited by their inability to synthesize lipids and are forced to survive in an environment with many sebaceous glands. *Malassezia need both saturated (palmitic acid*

(PA) and unsaturated acids (oleic acid (OA) to eat and live. PA and OA have fungicidal[19] *and fungistatic effect*[20] on *M. furfur*, and on *M. sympodialis at the same time. We might assume that skin fatty metabolism and Malassezia* colonization is a self-regulated system. Plus, not eaten oleic acid causes declension of epidermal differentiation, barrier defects and disorders of skin metabolism[21] and protein metabolites of Malassezia protect from UV light.[22] So is there a real need to get rid of fungus?

Oily and dry skin has always been associated with SD. This may indicate increased activity of the sebaceous glands and impaired function of the epidermal barrier. Instead, the decrease in lipid synthesis of sebocytes protects the epidermis from morphological changes caused by *Malassezia* and reduces dandruff. However, the role of sebum in the pathogenesis of SD remains controversial, since hyperactivity does not always cause dermatitis, and patients with SD may not have oily skin[23]. Some authors even suggest using "dermatitis of the sebaceous areas" than "seborrheic dermatitis" as a more precise term[24].

The aim of our study was to determine the factors that create the prerequisites for the development of dermatitis and overgrowth of Malassezia spp.

Materials and methods: Articles from Wiley online library, Cochrane library, Medline were analyzed**.**

Results. 1. Features of the sebaceous glands.

The holocrine type of sebaceous gland secretion (SG) is characterized by the fact that the glandular cell fills with fat and dies. The secret has been excreted on the surface of the epithelium near the hair follicles. Most SGs are focused on the face (especially the T-zone), the back, and the chest. Sebum acts as a delivery system for antimicrobial lipids, antioxidants, pheromone generation. It also serves as a substrate for bacterial and yeast growth[25].

2. There are numerous studies describing various forms of regulation of the sebaceous glands[26-29] and their effect on *Malassezia spp.* Let us look at some of them.

2.1. Endocrine regulation.

The hypothalamic-pituitary-adrenal system or axis (HPA) involves several neuro- and steroid hormones. Corticotropin-releasing factor or corticoliberin stimulates the release of adrenocorticotropic hormone (ACTH). HPA has shared receptors with the melanocortin system that regulate pigmentation and homeostasis. In addition to systemic regulation, the skin itself synthesizes some components of the HPA axis[30]. Therefore, it can be assumed that the sebaceous glands are regulated not only by systemic but also by autocrine impact of the skin.

Corticotropin acts directly on sebocytes. The introduction of ACTH to rats leads to enlargement of the sebaceous glands and intensification of their secretion. Interestingly, this effect is evident even in rats with removed adrenals. Therefore, ACTH can stimulate the sebaceous glands regardless of central regulation. In addition, ACTH is independent of the presence testicles and has no synergistic effect with testosterone. Alpha melanocyte stimulating hormone (α-MSG) also independently stimulates sebum secretion but exhibits a synergistic effect when is used with testosterone[31].

Prolactin is a pituitary neurohormone that regulates lactation and is dependent on the menstrual cycle. High levels of prolactin during pregnancy are reduced by childbirth but may be stimulated by breastfeeding. Interestingly, such hormone vacillations correlate with sebaceous gland secretion. It is believed that mom's aroma controls the behavior and reflexes of the baby[32]. Increased secretion is explained by the presence of prolactin receptors on sebocytes[33].

Abnormally high levels of prolactin can be observed in Parkinson's disease (PD) as well as excessive sebum production. Parkinson is a disease of dopaminergic neurons with dopamine deficiency. Seborrhea and hyperprolactinemia can be treated by restoring normal levels of dopamine through the administration of L-DOPA or using dopaminergic agonists[34].

Phenylketonuria (PKU) is another hypodopaminergic condition characterized by hyperprolactinemia and seborrhea and might be treated with L-DOPA[35].

Glucocorticoids enhance hair growth, stimulate sebocyte maturation and cause skin atrophy by acting on fibroblasts. Growth factors that exacerbate sebaceous gland diseases have a synergistic effect[36].

Growth hormone (GR) is produced mainly by somatotropic cells of the anterior pituitary gland. Acromegaly, as a manifestation of excessive GR in adulthood, is accompanied by increased sebum secretion. Conversely, GH deficiency is associated with abnormally low sebum secretion, which can be normalized after the use of substitution therapy. This conclusion was confirmed in a study demonstrating the presence of GR receptors on sebocytes[37].

Insulin-like growth factor has long been associated with weight loss diets. Low carbohydrate diets are known to have a positive effect in the treatment of acne. Hormone levels have been found to be positively correlated with sebum production[38].

Thyrotropic hormone (TTH), **triiodothyronine** (T3) and **thyroxine** (T4) are important hormones that regulate growth and development. It has been observed that hypothyroidism and thyroidectomy are associated with abnormally low sebum secretion. L-thyroxine replacement therapy partially normalizes the function of the glands, and thyrotoxicosis (hyperthyroidism) increases it excessively[39]. It tends to think that thyroid hormones act independently of androgens. TTH and T4 enhance the activity sebaceous glands even in castrated animals, and additional stimulation with testosterone does not produce a synergistic effect. TTH stimulation of animals with thyroid resection does not affect the sebaceous glands, which confirms the need in thyroid hormones. SG hyperstimulation is possible due to the presence of specific T3 receptors on their surface[40].

Androgens such as dehydroepiandrosterone (DHEA), androstenedione (A-dione) and testosterone stimulate sebum secretion in humans and increase gland size. The action of the active forms of androgens is mediated by their binding to nuclear androgen receptors. The absence of functional androgen receptors, for example, in general androgen insensitivity syndrome, impedes the action of androgens on skin appendages[41].

Therefore, skin synthesis and degradation of active androgens are noteworthy. It is known that precursors of active forms in tissues, such as DHEA DHEA and A-dione, are mainly synthesized by the glands, and testosterone and 5α-dihydrotestosterone (5α-DHT) in women are synthesized on the periphery. Androgens alone cannot affect sebocyte differentiation. They are activated by peroxisome proliferator-activated receptor (PPARs) ligands. Combining local hyperproduction of active androgens or an increase in blood 5α-DHT levels at normal levels of DHEA, A-dione, and testosterone may be the cause of sebum hyperproduction[42].

Estrogen β-receptors are present in keratocytes, melanocytes, fibroblasts and sebocytes, α-receptors have been found only in sebocytes in vitro. Estrogens reduce the activity of the sebaceous glands and are direct testosterone anagonists[43].

2.2. Neuropeptide regulation.

Nerve fibers due to release neuropeptides and neurotransmitters control epidermal proliferation, apoptosis, wound healing, inflammation, and melanogenesis. Eccrine glands and hair follicles are surrounded by a thick net of nerve endings. The presence of direct innervation of the sebaceous glands is noticeable in patients with partial paralysis of the face. The plegic side has increased sebum secretion and is more prone to acne[44]. The opposite effect is achieved by using topical antimuscarinic agents and botulinum toxin-A (Botox), which is used to reduce acne and sebum in humans[45]. Unfortunately, no study can accurately demonstrate the size and localization of nerve fibers that directly innervate the sebaceous glands. The possibility of indirect effects on the sebaceous glands by innervation of their ancestors near the hair follicles (HF) is considered. HF have a vast neural network that consists of a cluster of perifollicular and longitudinal nerve endings. The number of nerve fibers near the HF is demonstrated by the dependence of the allocation of fat on the hair growth cycle[46].

Acetylcholine directly affects the expression of cholinergic receptors in SG by stimulating muscarinic m2AChR and nicotinic receptors nAChRα7, nAChRα10 and nAChRβ4[47]. The increased sebum production on the face is observed after the application of acetylcholine and is directly proportional to the dose. Stimulation by non-neural sources of acetylcholine in the skin also should not be denied[48].

Adrenaline, as the major neurotransmitter of the sympathetic nervous system, does not affect the level of sebum secretion, which has been demonstrated by β-receptors blockade with Propranolol. And the sebaceous glands have neither β1- nor β2-adrenergic receptors[49].

Substance P (CP) is a neuropeptide of the tachykinin genius that modulates nociception, inflammation, and vasodilatation. CP-sensitive connective tissue fibers were found around the sebaceous glands, but only in patients with acne. Mice treated with CP developed expanded sebaceous glands and increased fat production. In humans it has also caused an increase of the level of interleukins and tumor necrosis factor. The inflammatory reaction disappeared with the introduction of dexamethasone. However, proven involvement of CP in the pathogenesis of inflammation is only available in patients with acne[50].

Neutrophins are proteins that regulate axonal growth and trophic supply of neurons. The sebaceous glands have receptors for neurotrophin -3 and nerve growth factor (NGF). Stress and inflammatory skin diseases induce NGF synthesis as opposed to healthy skin patients. Nevertheless, the role of neurotrophins in the regulation of skin fat production remains unknown but suggests the existence of a paracrine or autocrine mechanism of neurotrophin regulation of sebocytes[51]. An alternative version is an indirect action of neurotrophins by stimulating the growth of nerve fibers around the sebaceous cells of the progenitors of SG. In the experiment on skin, denervation led only to a slight decrease of hair growth, which may be an evidence of autocrine regulation rather than a direct enhancement of innervation[52].

Endocannabioids are unsaturated fatty acids. They are synthesized by the epithelium and modulate nociceptive and temperature sensitivity of skin nerves. Sebocytes have cannabinoid receptors and TRP channels (transient receptor potential channels). Activated endocannabinoid receptors modulate thermoregulation and enhance pain and itching sensations. Endogenous stimulation of these receptors leads to increased lipogenesis[53]. The effect of increasing endocannabinoid levels and phytocanabinoid (cannabigerol, cannabigerovarin) has been proposed as a treatment for inflammatory conditions accompanied by dry skin. In contrast to phytocannabinoids, cannabidiol, cannabichromen and cannabidivarin combine lipostatic, antiproliferative and anti-inflammatory effects and have the potential to treat acne acne[54].

Calcitonin gene-bound peptide (CGRP) is a calcitonin receptor that is also present on sebocytes[55].

2.3. Trait of the host.

Immunity, according to the literature, is a key weapon in the fight against *Malassezia* infections. Immunocompromised patients have seborrheic dermatitis much more often than healthy ones[56]. Skin affected by dermatitis is accompanied by increased immunoreactivity and high levels of IL-1α, I L-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, β-defensin, TNFα and IFNγ. Also, due to the increased degranulation of mast cells, there is a hyperproduction of histamine that accumulates in the epidermal layer. The DNA microarray test of patients with dandruff confirmed the

activity of inflammatory genes and showed decreased activity of genes controlling lipid metabolism[57]. Also, mice with activated 2C T-cell receptor had severe CD4 + and CD8 + T cell lymphopenia, and subsequently spontaneously developed a seborrheic skin phenotype. Similar abnormalities have been observed in HIV-positive patients, where it is known that the prevalence of SD is extremely high[56].

The microbiome of healthy skin differs from patients with seborrheic dermatitis. SD patients are mostly colonized by *Acinetobacter spp.*, *Staphylococcus spp*. and *Streptococcus sp*[58]. Among patients with dandruff, the most common are *Basidiomycota (Filobasidium spp.)* while among the healthy individuals *Ascomycota (Acremonium spp.)*[59]. Innate lymphoid cells (ILCs) affect commensal bacteria by modulating sebaceous gland activity in mice. Pools of ILC are found in all parts of the skin to inhibit sebocyte proliferation. In their absence, the sebaceous glands enlarge and more actively produce PA and OA. PA acid has specific anti-Gram-positive agents' activity. It is possible that with an excessive amount of substrate commensal Malassezia overgrows and triggers an inflammatory response but depresses a bacterial grows.

Skin barrier defects are associated with exacerbations of SD. Dry skin in winter and maceration most often violate skin protection. *Malassezia* modulates skin function directly through mediators or indirectly activate the immune response. It has been described that eradication of some *Malassezia spp.* makes ceramides, sphingolipids, histamine, and inflammatory markers in the skin return to norma[60].

Conclusions. The survival of *Malassezia* depends on the rate of adaptation to sweat, sebum, acidity, immune response, humidity, and environmental insolation, as well as the activity of other skin commensals – viruses, bacteria, microscopic fungi. *Malassezia* may trigger immune response but also protects our skin from UV-light, action of sebum and sweat and pathogenic bacteria. It is impossible to unambiguously identify the cause of inflammation of the skin in areas of large accumulation of sebaceous glands. Therefore, current treatment of patients with seborrheic dermatitis requires a personalized and predictive approach. Seborrheic dermatitis can be a marker of somatic diseases (see Table 1). *Malassezia* colonization in sebaceous areas is a consequence, not a cause of SD.

Table 1

Pathological conditions and disease having impact on seborrheic dermatitis

Diseases/ conditions	Sebum production	References	Article
Addison's disease	Sebum ↓	Goolamali SK (1974)	Sebum excretion and melanocyte-stimulating hormone in hypoadrenalism.
		Z Haut Geschlechtskr (1962)	Small-nodular sebaceous gland hypertrophy after cortisone treatment of Addison's disease.
Acromegaly	Sebum ↑	Resende M (2012)	Prevalence of dermatologic disorders in 15 patients with acromegaly.
		Borlu M (2012)	Acromegaly is associated with decreased skin transepidermal water loss and temperature, and increased skin pH and sebum secretion partially reversible after treatment.
Atopic dermatitis	Sebum normal or ↓ Malassezia spp. +	Agrawal K (2018)	Effects of atopic dermatitis and gender on sebum lipid mediator and fatty acid profiles.
		Ramos-E-Silva M (2018)	Red face revisited: Endogenous dermatitis in the form of atopic dermatitis and seborrheic dermatitis.
Bardet-Biedl syndrome	Sebum ↑	Haws RM (2019)	Cutaneous findings in Bardet-Biedl syndrome.
Hypothyroidism	Sebum ↓	Zouboulis CC (1998)	The human sebocyte culture model provides new insights into development and management of seborrhoea and acne.
Hashimoto autoimmune thyroiditis	Sebum ↓	Goucha S (2002)	Association of seborrheic pemphigus and Hashimoto autoimmune thyroiditis. Apropos of a further case
Hyperhidrosis	Sebum ↑	Mozaffari AA (2009)	Localized seborrhoeic dermatitis with hyperhidrosis due to mite infestation in an Iranian cross-breed ram.
Depression	Sebum ?	Maietta G (1990)	Patients with mood depression have a high prevalence of seborrhoeic dermatitis.
Tardive dyskinesia	Sebum ↑	Reuven Sandyk (1990)	Role of androgens in tardive dyskinesia.

Schizophrenia	Sebum ↑	Vassileva S (1990)	Familial occurrence of multiple seborrheic keratoses and schizophrenia.
		George A (2018)	A perspective study of cutaneous manifestations in primary psychiatric disorders in a tertiary care hospital.
Psoriasis	Sebum ↓ Malassezia spp. norma	Takahashi H (2014)	Defective barrier function accompanied by structural changes of psoriatic stratum corneum.
		Takemoto A (2015)	Molecular characterization of the skin fungal microbiome in patients with psoriasis.
Paget's disease	Sebum ↓ Malassezia spp. +	Shamsadini S (2006)	Surrounding ipsilateral eruptive seborrheic keratosis as a warning sign of intraductal breast carcinoma and Paget's disease.
		Sato Y (2019)	Malassezia-derived aryl hydrocarbon receptor ligands enhance the CCL20/Th17/soluble CD163 pathogenic axis in extra-mammary Paget's disease.
Parkinson's Disease	Sebum ↑ Malassezia spp. +	Trivedi DK (2019)	Discovery of Volatile Biomarkers of Parkinson's Disease from Sebum.
		Arsic Arsenijevic VS (2014)	A laboratory-based study on patients with Parkinson's disease and seborrheic dermatitis: the presence and density of Malassezia yeasts, their different species and enzymes production.
Phenylketonuria	Sebum ↑	Burton JL (1975)	An abnormality in sebaceous function in phenylketonuria.
Pregnancy	Sebum ↑	Burton JL (1970)	Effect of pregnancy on sebum excretion.
Dyslipidemia, obesity	No impact	Betul Imamoglu (2016)	Metabolic syndrome may be an important comorbidity in patients with seborrheic dermatitis.

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