



Seborrheic dermatitis: Etiology, risk factors, and treatments: Facts and controversies

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Abstract Seborrheic dermatitis (SD) is a common skin condition seen frequently in clinical practice. The use of varying terms such as *sebopsoriasis*, *seborrheic dermatitis*, *seborrheic eczema*, *dandruff*, and *pityriasis capitis* reflects the complex nature of this condition. Despite its frequency, much controversy remains regarding the pathogenesis of SD. This controversy extends to its classification in the spectrum of cutaneous diseases, having being classified as a form of dermatitis, a fungal disease, or an inflammatory disease, closely related with psoriasis. Some have postulated that SD is caused by *Malassezia* yeasts, based on the observation of their presence in affected skin and the therapeutic response to antifungal agents. Others have proposed that *Malassezia* is incidental to a primary inflammatory dermatosis that resulted in increased cell turnover, scaling, and inflammation in the epidermis, similar to psoriasis. The presence of host susceptibility factors, permitting the transition of *M furfur* to its pathogenic form, may be associated with immune response and inflammation. Metabolites produced by *Malassezia* species, including oleic acid, malssezin, and indole-3-carbaldehyde, have been implicated. SD also has been traditionally considered to be a form of dermatitis based on the presence of *Malassezia* in healthy skin, the absence the pathogenic mycelial form of *Malassezia* yeasts in SD, and its chronic course. As a result, proposed treatments vary, ranging from topical corticosteroids to topical antifungals and antimicrobial peptides.

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Introduction

Seborrheic dermatitis (SD) is a common, chronic, relapsing skin disease affecting the seborrheic areas of the body including the scalp, face (nasolabial folds, ears, and eyebrows), and upper part of the trunk (chest/presternal region). Some patients with SD also may present with inflamed erythematous folliculitis (possibly caused by *Malassezia*) and blepharitis.

Overall, SD affects 1% to 3% of immunocompetent adults, and it is more common in men than in women.^{1,2} SD occurs most commonly in infants within the first 3 months of life, in adolescents and young adults, with the incidence increasing again in patients older than 50 years of age.^{1,3,4} A cross-sectional case note study in a Greek teaching hospital between 1995 and 2002, reported 2035 patients diagnosed with SD, giving an overall relative prevalence of 4.05%.⁵ Comparisons with data from pediatric cross-sectional studies showed that the relative prevalence of SD in Greek outpatient children aged 0 to 15 years (2.5%) was lower than that in Indian⁶ (11.3%) and Chinese⁷ (3.2%) children, whereas in adults (4.05%), it was lower than

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Chinese⁷ (7%), similar to Iranian,⁸ and higher than British populations⁹ (2.35%).

SD is increasingly being recognized to have a substantial negative effect on the patient's quality of life (QoL). In a study of 3000 patients with SD and/or dandruff, patients with dandruff had significantly better QoL than patients with SD or patients with SD plus dandruff ($P < 0.001$ for both comparisons).¹⁰

The use of varying terms such as *sebopsoriasis*, *seborrheic dermatitis*, *seborrheic eczema*, *dandruff*, and *pityriasis capitis* reflects the vast clinical spectrum of SD and the controversy regarding its etiology, being considered at times a form of dermatitis, a precursor of psoriasis or a fungal disease.^{1,10} Diagnosis remains a clinical one, based on the characteristic clinical morphology of erythema and scaling and the distribution of lesions on the scalp (Figure 1), nasolabial folds, eyebrows, postauricular areas, and the sternum. The distribution of lesions is generally symmetrical. Absence of a standardized definition of SD has been an obstacle to scientific investigation and its differentiation from dandruff.¹¹ Dandruff can be considered a mild form of SD, with scalp scaling and/or mild to marked erythema of the nasolabial fold during times of stress.^{10,12} The severity of SD varies. Some patients experience only a mild flaking dandruff, whereas others demonstrate a severe oily, scaling on the scalp, face, and trunk.¹²

Etiology of seborrheic dermatitis: facts

SD is a multifactorial skin disease that needs endogenous and exogenous predisposing factors for its development. The fact that SD is more common in men and that, except in infants, it begins to develop at puberty, suggests a significant hormonal influence, mainly of androgens.^{1,13} The age prevalence of SD coincides with the period of life when sebaceous glands are most active; moreover, SD lesions are located in sebaceous gland-rich body areas. The skin surface



Fig. 1 Erythema and extensive scaling on the scalp.

lipid composition in males with SD has been shown to differ from that of unaffected controls.¹²

Another reported important pathogenic factor is a *Malassezia* infection. Its role in SD has been supported by the fact of positive correlation between yeast density on the skin and the severity of SD, as well as a high therapeutic efficacy of antifungal agents in SD.^{1,13}

The fact of a higher incidence of SD in HIV-positive patients implies the contribution of an immunologic defect.¹ Major textbooks report seborrheic dermatitis in the chapter on cutaneous changes of altered reactivity together with atopic dermatitis and nummular dermatitis¹⁴ or in the chapter on eczematous eruptions.¹⁵

Established risk factors for seborrheic dermatitis

SD is much more common in immunosuppressed patients, such as organ transplant recipients,¹⁶ patients with HIV/AIDS,^{17–19} chronic alcoholic pancreatitis,²⁰ hepatitis C virus,²¹ and various malignancies,²² with rates up to 83%¹⁷ compared with 1% to 3% seen in the general population, suggesting that the immune system is important in the pathogenesis of the disease.²³ SD also is more common in patients with neurologic and psychiatric diseases, including Parkinson's disease,^{24,25} tardive dyskinesia, and mood depression,^{1,26–28} and in patients with genetic disorders, such as Down syndrome,²⁹ Hailey–Hailey disease,³⁰ and cardiofaciocutaneous syndrome.³¹

Because patients with unilateral Parkinsonism may have bilateral seborrhea, the mechanism underlying changes in skin sebum levels is probably endocrine rather than neurotrophic.^{32–34} This hypothesis is supported by a study that found an elevated circulating α -melanocyte stimulating hormone in patients with Parkinson's disease.³⁵ SD often has a seasonal pattern, with increasing presentation during the winter. Exposure to sunlight typically improves SD;³⁶ however, there are cases of SD development subsequent to psoralen plus ultraviolet A therapy.³⁷

Etiology of seborrheic dermatitis: controversies

Seborrheic dermatitis: the *Malassezia* theory

Louis-Charles Malassez (1842–1909) first proposed the connection between fungi and SD in 1874.³⁸ Lipophilic yeasts of the genus *Malassezia* (former *Pityrosporum*) are commensals of the microbiota found on normal skin of 75% to 98% of healthy adults, and they possess the ability to metabolize fatty compounds in sebum. These yeasts are the cause of pityriasis versicolor and *Malassezia* folliculitis and appear to be involved in the pathogenesis of common skin disorders, such as SD, psoriasis, and atopic dermatitis.³⁹ A direct causal link between *Malassezia* yeast and SD has been proposed based on the distribution of *Malassezia* species on

the skin of lipid-rich anatomic locations, such as the face, scalp, and trunk,⁴⁰ on the presence of *Malassezia* in affected SD skin, and on the therapeutic response seen to antifungal agents.¹¹ Improvement in SD is accompanied by reduction in the yeast on the scalp, whereas recolonization leads to disease recurrence.^{41–43} A causative link between SD and *Malassezia* was further supported by the finding that patients with dandruff who had responded to nystatin relapsed when nystatin-resistant *Pityrosporum* (*Malassezia*) was reintroduced⁴⁴; moreover, diseases associated with *Malassezia* species such as pityriasis versicolor⁴⁵ and *Pityrosporum* folliculitis,⁴⁶ also are commonly found in patients with SD.

Malassezia yeasts have been associated with a number of different diseases, either directly via tissue invasion as in pityriasis versicolor, or indirectly through possible immunologic mechanisms, as in SD.^{11,47} Unlike pityriasis versicolor, in which *Malassezia* yeast can be seen under the light microscope in its pathogenic mycelial phase,^{48,49} in all other cutaneous diseases, neither the number of yeasts nor their morphology are related to the skin lesions. SD is not associated with these microscopic changes, and it remains unclear whether or not SD patients have higher *Malassezia* counts than normal controls,^{50,51} although a correlation between yeast density and severity of SD has been reported.⁵²

Among the 13 *Malassezia* species recognized to date (*M furfur*, *M obtusa*, *M globosa*, *M slooffiae*, *M sympodialis*, *M pachydermatis*, *M restricta*, *M yamatoensis*, *M nana*, *M japonica*, *M equine*, *M caprae*, and *M dermatis*), *M restricta*, and *M globosa* are considered the most important pathogenic organisms in the development of SD, although some reports have also implicated *M furfur*, *M sympodialis*, *M obtusa*, and *M slooffiae*.^{39,53–58} Studies have been performed to determine whether the amount and/or species of *Malassezia* found on the skin of SD patients is different from that in normal controls. One study⁵⁹ found that the predominant species in SD patients was *M globosa*, as opposed to *M sympodialis* in normal skin. Another study⁶⁰ found *M globosa* and *M restricta* on diseased skin but primarily *M globosa* in controls. A third study⁶¹ found *M sympodialis* in patients with SD and in controls. Some have stated that *M globosa*^{55,59,60,62} predominate, whereas others have found *M restricta*^{48,63–65} or *M sympodialis*⁶⁶ to be the most common species in lesions of SD. The variation of the relative prevalence of the six lipophilic species according to geographical region may, at least in part, explain these conflicting results.

Analyses of the complete genome of *M globosa* and the partial genome of *M restricta*⁵⁸ have presented gene-encoding enzymes of the lipase and phospholipase families that could explain the lipid dependency of the genus. The secretion of enzymes by human pathogenic fungi has been considered an important factor in the invasion and dissemination in the host; thus, it is suggested that lipases and phospholipases are involved in the mechanisms of pathogenicity of *Malassezia* species.^{58,67} It was proposed

that lipases may be related to the development of SD and could be considered as virulence factors. Some authors suggest that these enzymes provide the ability to metabolize lipids and to integrate the fatty acids into the fungal cell wall, and thus are very important for growth.⁶⁷

It is also now possible to subtype *Malassezia* species such as *M globosa* into different genetic groups. Not all *M globosa* or *M restricta* strains can be isolated from SD,⁵⁵ suggesting that there may be specific strain-determined phenotypic characters of different fungi that account for their ability to cause disease.¹¹

Skin scrapings and mycologic analysis⁵⁵ have shown that patients with SD usually carry an increased number of *M furfur* compared with SD-free individuals. The exact mechanism by which the skin lesions are induced remains unknown. Positive patch test reactions to *M furfur* are frequently observed in atopic dermatitis and less frequently in patients with SD.^{68–70} In addition to 20 indole derivatives, *M furfur* produces *Malassezin* when L-tryptophan is the single nitrogen source in the culture medium. *Malassezin* induces apoptosis in cultured human melanocytes through activation of the aryl hydrocarbon receptor (AhR). Synergism of *Malassezin* with the other indoles is considered responsible for the clinical aspects of pityriasis versicolor, as is hypopigmentation, resistance of pityriasis versicolor lesions to ultraviolet radiation (pityriacitrin), and downregulation of the inflammatory response (pityriarubins).⁴⁷

Seborrheic dermatitis: the hyperproliferative theory

In past years, it was proposed that the yeasts were incidental to a primary inflammatory dermatosis. This resulted in increased cell turnover and inflammation in the epidermis, similar to psoriasis.^{71,72}

Evidence used in favor of the hyperproliferative theory included the failure of patients with dandruff to respond to topical amphotericin B and the response to keratolytic and anti-inflammatory medications, such as salicylic acid and corticosteroids.^{72,73} Also, psoriasis is an inflammatory skin disorder sharing some clinical characteristics with SD. Psoriasis presents with well-defined, erythematous scaly patches, with thick silvery scale on the scalp, trunk, and limbs, especially on the elbows and knees. When both psoriasis and SD are localized exclusively on the scalp with no involvement of other skin sites, even a skin biopsy may not accurately discriminate between these two conditions. A retrospective observational study evaluated hand-held dermoscopy as a valuable method to differentiate between scalp psoriasis and SD. Three features of the vasculature were associated with scalp psoriasis, namely, red dots and globules ($P < 0.0001$), twisted red loops ($P = 0.003$), and glomerular vessels ($P < 0.0001$), corresponding to the tortuous and dilated blood vessels within the elongated dermal papillae in psoriasis. The arborizing vessels ($P < 0.0001$) and atypical red vessels ($P = 0.024$) seen in SD

represent ectatic subpapillary plexus in the slightly hyperplastic rete ridges.⁷⁴

Seborrheic dermatitis: a form of dermatitis? The immunologic link

SD is more common in immunosuppressed patients, suggesting that immune mechanisms are important in the pathogenesis of the disease.^{17,75,76}

Recently, a DBA/2 2C TCR transgenic mouse was found to develop a localized inflammatory skin disease on maturity, with striking skin scaling very similar to SD.⁷⁷ These mice do not have T-cell progenitor thymocytes and are lymphopenic for both CD4+ and CD8+ cells. Yeast-like organisms are seen in affected hair follicles, and the condition responds to treatment with fluconazole. These organisms have not been yet isolated from the lesions and they have not been characterized; nevertheless, the association of a scaly dermatosis with a model of immunodeficiency parallels SD characterized or in HIV-positive patients.⁷⁷

Humoral as well as cellular immunity has been studied in patients with SD with conflicting results. With regard to cellular immunity, one study⁷⁸ found a low CD4+/CD8+ ratio in 68% patients, whereas another study⁷⁹ found a normal ratio in all patients with SD. Another study⁷⁵ also found a normal CD4+/CD8+ ratio, but reported reduced number of B cells in 28% patients and an increased number of natural killer cells in 48% patients. Increased percentages of CD8+ T cells was found in 60% of patients and a decrease in the percentages of CD4+/CD8+ ratio in 70 patients, which suggest that SD patients show an impaired cellular immunity. The alteration in the CD8+ T-cell subpopulation may result in cytokine release.²³ In patients with SD, no specific defects in T-cell function have been shown to explain the link with HIV infection, nor is there evidence of contact sensitization in SD patients.⁵⁶

The results of a study showed that *Malassezia* yeast significantly reduces the production of pro-inflammatory cytokines,⁸⁰ which is related to the presence of lipid-rich microfibrillar layer surrounding yeast cells. High quantity of lipid may prevent the yeast cell from inducing inflammation in consistence with their commensal status. Further study by the same group demonstrated that extraction of cell wall lipids reversed their capacity to reduce the level of pro-inflammatory cytokines.⁸¹ In SD, however, these yeast fail to possess lipid layer because of alterations in the availability of nutrients on the lipid surface.⁸² An altered lipid layer in SD may explain the inflammatory nature of the disease.⁶⁵

A study of 54 patients diagnosed with SD compared with 54 healthy controls, assessed oxidative stress status and measured serum total antioxidant status (TAS), total oxidative status (TOS), and the oxidative stress index (OSI). The mean TAS values were significantly lower in the patient group ($P = 0.024$), and patients had significantly higher TOS and OSI values than controls ($P < 0.05$). There

was no correlation between SD severity and TAS, TOS, and OSI values. The authors concluded that oxidative stress, either due to overproduction of oxygen radicals (reactive oxygen species or inadequate antioxidants), may contribute to the pathogenesis of SD.² Reactive oxygen species cause lipid peroxidation in the cell membrane, DNA damage, and the secretion of inflammatory cytokines, eliciting an immune and inflammatory response.⁸³ Immunohistochemical studies in patients with SD have shown increased production of cytokines such as interleukin (IL)-1a, IL-1b, tumor necrosis factor alfa, interferon- γ , IL-12, and IL-4 in the lesional skin compared with non-lesional skin.⁸⁴ A significant increase in the ratio of IL-1RA: IL-1a and IL-8 and overproduction of histamine have been detected in the scalp skin of patients with dandruff and SD compared with healthy individuals⁸⁵; however, although the ratio and quantities of some cytokines were different from those expressed in non-SD controls they were not significantly different from those seen on normal skin of patients with SD.⁸⁶ The study of inflammatory cytokine stimulation by *Malassezia* is complex particularly because lipids protecting the yeast cell wall appear to modulate the immune-stimulating capacity of *Malassezia* species.⁸⁷ An hypothesis is that failure to suppress an inflammatory response to a surface commensal yeast results in its "activation" and in the development of SD.

SD represents an exaggerated response to *Malassezia* yeast

M. furfur is a non-pathogenic skin commensal that can undergo transition to a pathogenic form under favorable conditions.⁸⁸ At high concentrations, it reduces the protective barrier of the skin and affects the control of inflammation.⁸⁹ The presence of host susceptibility factors associated with immune response and inflammation could explain the lack of correlation between the presence and number of yeasts and the presence and severity of dandruff.

DNA microarrays were used to create a detailed molecular picture of dandruff lesional skin in 15 patients compared with non-dandruff individuals. The most striking feature of lesional dandruff scalp skin relative to normal was the reciprocal expression of induced inflammatory genes and repressed lipid metabolism genes. Induced inflammatory genes also were enriched in dandruff uninvolved skin, suggesting the existence of predisposing factors associated with inflammation.⁹⁰ The expression of the gene-encoding fatty acid synthase, the rate-limiting enzyme in fatty acid biosynthesis, was diminished by nearly 50% in dandruff lesional skin versus non-dandruff.⁹¹

Metabolites produced by *Malassezia* species may play a key role. The current hypothesis for SD/dandruff pathogenesis associates individual susceptibility with the penetration of irritating *Malassezia* metabolites, such as oleic acid, through a defective epidermal barrier.⁹² This is further supported by the nonspecific immune response to

Malassezia yeasts²³ and the similar *Malassezia* counts in SD patients and controls.⁹³ *M globosa* is capable of generating oleic acid through lipase activity, and the desquamation seen on dandruff skin can be produced by oleic acid, in dandruff-susceptible individuals. In SD, *Malassezin* and indole-3-carbaldehyde, both involved in immune regulation, were only produced on the skin of patients with SD associated with *M restricta*. These compounds are ligands for the AhR that also have been implicated in immunologic events such as the differentiation of Th17 cells and the production of inflammation and mediation of contact sensitivity in transgenic mice.^{47,94} It was found that compared with healthy controls (n = 7), bioactive indoles that are AhR agonists are selectively produced by *M furfur* isolates from SD patients (n = 10).⁴⁷ In SD, the lipophilic *Malassezin* and indolo[3,2-b]carbazole could cross the defective epidermis,⁹² reach the granular and spinous layers, and activate the AhR. Subsequent downregulation of the high-affinity epidermal growth factor receptor⁹⁵ could trigger SD.⁹⁶

In SD, proliferation of *Malassezia* species, which are commensal yeasts, appears to trigger an immunologic response, which stimulates inflammation that precipitates flares of SD, although the inflammatory pathway in SD is not well defined.⁵³

Treatments

Although SD has no permanent cure, a variety of treatment options are available that can effectively treat this condition. Therapy centers on the control of acute flares and on maintaining remission with long-term therapy. Efficacy, ease of use, safety, and compliance issues need to be considered when selecting a treatment to provide the best clinical outcome. The age of the patient is also an important consideration.

Established treatments include symptomatic therapies such as keratolytics and etiologic therapies, such as topical corticosteroids and antifungals. Controversial emerging therapies include topical calcineurin inhibitors, metronidazole, and antimicrobial peptides.

Topical urea is a known keratolytic^{97,98}; propylene glycol is used as an excipient and has keratolytic effects; lactic acid has keratolytic and hydrating properties; and all these agents also inhibit the growth of bacteria and/or fungi.⁹⁹ A topical keratolytic-containing urea, propylene glycol, and lactic acid, applied daily for 4 weeks, was assessed for the treatment of mild to severe SD of the scalp, in 88 patients, in two randomized, double-blind, placebo-controlled, multicenter trials, and significant improvement in erythema and desquamation was shown ($P < 0.05$).⁹⁷

Topical antifungals^{100,101} or topical corticosteroids¹⁰⁰ are generally the first line treatment for SD and are sometimes used in combination.^{100,102} Topical antifungals are used in the treatment of SD because of their ability to reduce *Malassezia* proliferation and the subsequent inflammatory

response.¹⁰³ Topical antifungals are safe to use for all skin areas, even thin, sensitive skin, and in infants. They can be used as a component of combination topical therapy, often in conjunction with a topical corticosteroid,¹⁰² to provide an antifungal effect that complements the anti-inflammatory activity of the topical corticosteroid.³ A randomized controlled, investigator-blinded study in 326 patients with moderate to severe scalp SD, reported that the combination therapy of twice-weekly clobetasol propionate shampoo 0.05% alternating with twice-weekly ketoconazole shampoo 2% for 4 weeks, was more efficacious than ketoconazole shampoo monotherapy.¹⁰² Also topical azoles including bifonazole 1% ointment (with or without urea), ketoconazole 2% cream or shampoo, and fluconazole 2% shampoo, have been shown to be effective and well tolerated.¹⁰⁴ Some strains of *M globosa* and *M restricta*, the causative agents most associated with dandruff and SD, are resistant to azole antifungals, explaining treatment failure seen in clinical practice.¹⁰⁵

Pyrithione is a zinc ionophore, facilitating zinc transport across membranes. Zinc pyrithione inhibits fungal growth through increased cellular levels of copper, damaging iron-sulphur proteins that are essential for fungal metabolism.¹⁰⁶ Ciclopirox olamine 1% (shampoo, cream, and gel) is a broad-spectrum antifungal agent, also exhibiting anti-inflammatory effect, that has been shown to be effective for SD of the scalp and face.¹

Selenium sulfide has also been used for SD treatment due to its fungicidal activity to *P ovale* and keratolytic effects. It is available in various formulations, such as shampoo, lotion, cream, foam, and suspension. Orange-brown scalp discoloration has been described in children after the application of selenium sulfide 1% shampoo for SD. It was stated that this side effect should be borne in mind and not be confused with Langerhans cell histiocytosis. This discoloration was reversible and easily removed with an isopropyl alcohol swab.¹⁰⁷

Topical calcineurin inhibitors have been used for patients with SD because of their immunomodulatory and anti-inflammatory properties.¹⁰⁸ Tacrolimus 0.1% ointment has been reported to be effective in SD in small case series.^{109–111} In an open-label trial of 83 subjects with scalp SD, tacrolimus was as effective as betamethasone lotion or zinc pyrithione shampoo; however, tacrolimus offered more prolonged remission compared to topical betamethasone.¹¹² Tacrolimus 0.1% ointment was compared with hydrocortisone 1% ointment for the treatment of facial SD in adults (n = 30), in a Phase II, single-center, single-blind, randomized controlled, 12-week trial. At week 12, both hydrocortisone 1% ointment and tacrolimus 0.1% ointment groups showed a similar and statistically significant improvement and they were well tolerated.¹¹³ Also, pimecrolimus has showed comparable efficacy with topical corticosteroids and topical antifungals.^{114–116}

A randomized controlled, blinded study in 60 patients with facial SD showed that metronidazole 0.75% gel applied

for 4 weeks, had similar efficacy (63% mean percentage decrease in clinical disease severity scores) and safety profile to ketoconazole 2% cream. The rationale of use of topical metronidazole is its anti-inflammatory action via inhibition of free radical species and subsequent oxidative tissue damage.¹¹⁷

Regarding systemic therapies, oral antifungals have been used in selected cases of extensive SD resistant to topical therapies. Oral ketoconazole, 200 mg daily for 4 weeks, was effective for SD of the scalp and body. Itraconazole 200 mg daily for 7 days has been shown to also be effective. An advantage of itraconazole is the reported reduced risk for hepatotoxicity compared to ketoconazole.¹ In view of the fact that oral terbinafine (a fungicidal allylamine) is not effective for pityriasis versicolor, a skin disease caused by *Malassezia* species, this agent is not used for SD.¹

For infantile SD, a moisturizer containing 0.025% licochalcone was compared with 1% hydrocortisone, for 14 days, in a prospective, split-side, double-blind study in 72 infants (ages 2 weeks to 1 year). These two treatments showed similar response rates (90%; $P = 0.317$). Licochalcone is an extract from *Glycyrrhiza inflata*. It is a natural product that has anti-inflammatory and antimicrobial effects.¹¹⁸

Antimicrobial peptides (AMPs) are an emerging concept as an innate defense mechanism of the epithelial barrier. Cathelicidins and other cationic AMPs are active against *M. furfur*.^{119,120} Cecropin A (CA) and magainin 2 (MA) are non-cytotoxic AMPs acting via the formation of ion channels, with subsequent disruption of bacterial phospholipid bilayers and eventual cell death. A modified synthetic AMP, P5, which is a synthetic CA-MA hybrid peptide analogue, was studied against *M. furfur* in normal human keratinocytes. P5 showed potent antifungal action, and it was three to four times more potent against *M. furfur* than ketoconazole or itraconazole *in vitro*. Also, it had anti-inflammatory properties, inhibiting the expression of IL-8 and Toll-like receptor 2 in *M. furfur*-infected human keratinocytes, and downregulating nuclear factor- κ B activation and intracellular calcium fluctuation.⁸⁹

Some therapies are better suited for treatment of the acute flare, whereas others are more adaptable for long-term maintenance therapy to reduce the frequency and intensity of exacerbations.³ Topical corticosteroids should be reserved for the control of acute flares. Topical corticosteroids should be used in a limited body area and for a short period of time, with extra caution being paid when treating children. Patients should be advised to follow the application instructions and not to extend the duration of treatment beyond what is recommended, to avoid permanent side effects such as skin atrophy and telangiectasias.³ The 2% shampoo formulation of ketoconazole (ketoconazole shampoo 2%, KC) also has been used successfully as a prophylactic treatment to prevent recurrence of the disease symptoms¹²¹ and as maintenance therapy (once weekly) to sustain clinical improvement.¹⁰² More studies also may be conducted to further evaluate

topical pimecrolimus and tacrolimus as a long-term maintenance therapy for SD.

Conclusions

SD is a common skin condition seen frequently in clinical practice. Despite its frequency, much controversy remains regarding its pathogenesis. This controversy extends to its classification in the spectrum of cutaneous diseases, having been classified as a form of dermatitis, or a fungal disease, or a disease closely related with psoriasis. As a result, treatments vary, ranging from topical corticosteroids to topical antifungals and AMPs. These scientific questions are yet to be answered. Research in the pathogenetic mechanisms underlying SD development will shed light on its etiology and may open the way for the use of optimal etiologic therapies.

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