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Sunscreens in the Management of Photodermatoses

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ABSTRACT

Key to the management of photodermatoses is photoprotection, which includes seeking shade; wearing photoprotective clothing, wide brimmed hats, and sunglasses; and applying sunscreens. The process of selecting the most effective sunscreen depends on identification of the wavelengths of photons that are responsible for inducing the sensitivity reaction, which can be determined through assessment of patient history or by phototesting. Sunscreens with sun protection factor (SPF) >30 that incorporate photostable or photostabilized ultraviolet A (UVA) filters (labeled as "broad spectrum" in the US) are usually the appropriate choice for adequate photoprotection.

Key words: photodermatoses, photoprotection, photosensitivity disorders, sunscreen, UVA, UVB

Photodermatoses are a group of diseases involving abnormal cutaneous reactions to solar radiation. They include immunologically mediated photosensitive disorders, drug or chemical induced photosensitivity reactions, DNA repair-deficiency photodermatoses, and photoaggravated dermatoses.[1] While these diseases have different pathophysiologic mechanisms, not all of which have been clearly defined, photoprotection is an integral part of their management. Photoprotection includes seeking shade, wearing photoprotective clothing, a wide brimmed hat, and sunglasses, as well as applying broad spectrum sunscreens with sun protection factor (SPF) >30.[1-3]

Choice of Sunscreen Protection

The method by which the clinician chooses the most effective sunscreen for each patient depends on identification of the photon wavelength responsible for inducing the sensitivity reaction, i.e., the action spectrum.[3] This can often be ascertained through the determination of minimal erythema dose to ultraviolet B (UVB) (280-320 nm) (MED-B) and ultraviolet A (UVA) (320-400 nm) (MED-A), and though the induction of lesions by UV or visible light (400-700 nm).[2,3] The fact that window glass filters out UVB, but not longwave UVA, also helps to determine the action spectrum of the patient's photosensitivity disorder.

In the United States, UVB and UVA filters are categorized into organic and inorganic filters (Table 1). While there are many excellent UVB filters, there are only a limited number of organic UVA filters available in the US, namely the benzophenones (oxybenzone, dioxybenzone, and sulisobenzone), butyl methoxydibenzoylmethane (commonly known as avobenzone), and methyl anthranilate.[1,3] All, with the exception of avobenzone, are primarily protective only against UVA-2 (320-340 nm). The absorption of avobenzone extends into UVA-1 (340-400 nm).[1,3] However, because avobenzone is photolabile, degradation occurs rapidly upon exposure to sunlight. In the past few years, technology has been developed to photostabilize avobenone. This can be achieved by combining it with photostable UV filters, such as octocrylene, salicylates, or oxybenzone; in some products non-UV filter photostabilizing compounds, such as diethylhexyl 2,6-naphthalate (DEHN), diethylhexyl syringylidene malonate (Oxynex® ST), or caprylyl glycol are also used.[1] Ecamsule (Mexoryl™ SX) is a photostable organic short UVA filter (with maximum absorbance at 344 nm) that was approved by the US FDA in 2006 only as a component of certain sunscreen products.[4] The approved inorganic sunscreens or physical blockers are titanium dioxide and zinc oxide, which offer protection from UVB to visible ranges. They are used in micronized form to improve cosmetic acceptability.[1,3] However, it should be noted that the micronized form protects only in the UVB and UVA spectrums, but not in the visible range.

The SPF value for sunscreens reflects the ability of the product to protect against UV-induced erythema, which is primarily the effect from UVB exposure, and to a lesser extent from UVA-2. While there are rating systems used in many other countries to grade the protectiveness of sunscreens against

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UVA, currently, the FDA has not yet finalized the revised rating system that will be implemented in the US. Consumers should look for sunscreens that provide "broad spectrum" protection, which would indicate that the formulations contain UVA filters. However, as noted above, since many UVA filters do not cover longwave UVA (UVA-1), and not all sunscreens incorporate a photostabilized UVA-1 filter (i.e., avobenzone), the current UVA rating system used in the US reveals significant shortcomings.

Sunscreens and Photodermatoses

Herein, the use of sunscreens in the management of photodermatoses (polymorphic light eruption and solar urticaria) and photoaggravated dermatosis (lupus erythematosus) is outlined.

Polymorphic Light Eruption (PMLE)

PMLE is the most common photodermatosis, with prevalence as high as 10-20%, typically starting during the second and third decades of life.[1,3,5,6] Lesions develop within hours of sun exposure, usually resolve in a few days, and do not scar. PMLE is generally most severe in the spring or early summer and a genetic predisposition appears to be a likely risk factor.[5,6] The pathogenesis is thought to be attributable to the failure of normal UV-induced immunosuppression, which results in enhanced reactivity to UV triggered photoallergens in the skin.[1,5,6] Photoprovocation tests have shown that PMLE was induced by UVA in 59% to 94.2% of cases, and UVB in 23% to 40%.[6-9] Induction by a combination of UVA and UVB was observed in 18% to 90% of patients, depending on the methodology used in the photoprovocation tests.[6,7,9]

Because most sunscreens protect predominantly against UVB, and therefore, fail to prevent PMLE,[6-9] the need to study sunscreens with high UVA protection, through the use of photostable UVA filters, was fostered.[8,9] In a retrospective study of 133 patients with PMLE, the complete follow-up information on photoprotection was available for 79 subjects. The data revealed that the use of a sunscreen with a mean SPF of 14 did not prevent skin lesions in 88% of these patients.[7] Another study using a sunscreen with high SPF and high UVA-PF (UVA protection factor), containing photostable UV filters (Tinosob® M, Tinosorb® S) and photostabilized avobenzone, showed that it protected against the development of lesions in 69% of subjects with PMLE after standardized photoprovocation.[8]

Other trials have compared the efficacy of two sunscreens with similar SPF, but different levels of UVA protection. In an indoor, bilateral comparison study, 14 volunteers used a product with SPF 60 and UVA-PF 15 (containing avobenzone, Mexoryl™ SX, Eusolex®, and micronized titanium dioxide) on one side of the chest, and the other side received another product with SPF 50 and UVA-PF 4 that contained titanium dioxide and zinc oxide. Following photoprovocation, only two subjects developed new PMLE on the side treated with the higher UVA-PF sunscreen, while 14 subjects developed new lesions on the other side.[4] In an outdoor study, 16 female subjects susceptible to PMLE were exposed daily to sunlight for 7 days after using two products with similar SPF 60+, but different UVA-PF values on each half of the body. Fifteen subjects experienced eruptions with the photounstable lower UVA protection (UVA-FP 4) product, compared with only

Filter Type	Name of UV Filter		Concentration
Organic UVB Filters	Cinnamates	Octinoxate (octyl methoxycinnamate, Parsol MCX)	7.5%
		Cinoxate	3%
	PABA derivatives	Para-aminobenzoic acid (PABA) 15%	15%
		Padimate O (octyl dimethyl PABA)	8%
	Salicylates	Octisalate (octyl salicylate)	5%
		Homosalate	15%
		Trolamine salicylate	12%
	Others	Octocrylene	10%
		Ensulizole (phenylbenzimidazole sulfonic acid)	4%
Organic UVA Filters	Benzophenones	Oxybenzone (benzophenone-3)	6%
		Sulisobenzone (benzophenone-4)	10%
		Dioxybenzone (benzophenone-8)	3%
	Others	Butyl methoxydibenzoylmethane (avobenzone, Parsol 1789)	3%
		Meradimate (menthyl anthranilate)	5%
Inorganic Filters	Titanium dioxide		25%
	Zinc oxide		25%

Table 1. Sunscreen active ingredients listed in the US FDA monograph[10]

four patients exhibiting eruptions with the photostable high UVA (UVA- PF 28) sunscreen.[4]

Solar Urticaria (SU)

SU is an uncommon photodermatosis, often occurring in the third decade of life and demonstrating a female preponderance.[9,11,12] Urticaria is a mast cell-mediated disease that can develop within minutes after exposure to sunlight.[9,11,12] The action spectrum includes UVA, UVB, and visible light.[9]

Because there is no sunscreen product available that adequately protects against visible light, photoprotection in SU induced by visible light can only be achieved with physical measures, such as clothing, which in one study resulted in symptomatic control in 84% of patients.[9] Broad spectrum high SPF sunscreens are helpful for SU that is triggered by UVA and/or UVB.

Lupus Erythematosus (LE)

LE is the most common photoaggravated dermatosis.[13,14] Following UV exposure, skin lesions develop within days or up to weeks after and can persist for months.[14] Tumid LE is the most photosensitive subset, followed by subacute cutaneous LE, systemic LE, and discoid LE. Sunlight exposure can even induce systemic disease activity.[14] Provocative phototesting by Kuhn et al. produced characteristic skin lesions in 175 of 323 LE patients; 42% were reactive to only UVB and 34% to UVA only.[13] Of the patients receiving combination UVA + UVB irradiation, 53% exhibited positive photosensitivity reactions.

The study performed by Stege et al.[15] tested the efficacy of three distinct sunscreens to prevent the UV radiation-induced generation of skin lesions in photosensitive LE patients by employing a standard provocative phototest.[15] The 11 patients developed LE-specific skin lesions upon photoprovocation with a combination of UVA and UVB radiation. The same group was tested with three different sunscreens. The most effective was a product with high SPF and high UVA-PF (UVB filter: octocrylene; UVA filters: Mexoryl™ SX, Mexoryl™ XL, avobenzone, and titanium dioxide), which protected 11 of 11 patients. Five patients were protected by a product with similar SPF, but medium UVA-PF (UVB filters: Eusolex® 6300, Parsol® MCX, Uvinul® T150, Neohelipan®; UVA filter: avobenzone; titanium dioxide) and only three by a product with the lowest SPF and lowest UVA-PF (UVB filters: Eusolex® 6300, Parsol® MCX, Uvinul® T150; UVA filter: avobenzone; titanium dioxide). While several of the filters used in the study are not commercially available in the US, this trial does indicate that sunscreens with high SPF and high UVA-PF are necessary for the management of patients with photosensitive LE.[15]

Conclusion

Sunscreens are an integral component of photoprotection in the management of photodermatoses. UV filters are broadly categorized into organic UVB and UVA filters, and inorganic filters. The efficacy of sunscreens has been well documented in PMLE, solar urticaria, and lupus erythematosus.

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Smoking and Skin Disease

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ABSTRACT

Tobacco smoking is a serious and preventable health hazard that can cause or exacerbate a number of diseases and shorten life expectancy, but the role of smoking as an etiologic factor in the development of skin disease is largely unknown. Although epidemiological evidence is sparse, findings suggest that tobacco smoking is a contributing factor in systemic lupus erythematosus, psoriasis, palmoplantar pustulosis, cutaneous squamous cell carcinoma, hidradenitis suppurativa, and genital warts. In contrast, smoking may confer some protective effects and mitigate other skin diseases, notably pemphigus vulgaris, pyoderma gangrenosum, aphthous ulcers, and Behçet's disease. Various degenerative dermatologic conditions are also impacted by smoking, such as skin wrinkling and dysregulated wound healing, which can result in post-surgical complications and delayed or even arrested healing of chronic wounds. Most likely, alteration of inflammatory cell function and extracellular matrix turnover caused by smoking-induced oxidative stress are involved in the pathophysiologic mechanisms.

Key words: Tobacco smoking, skin diseases, risk factor

Pathophysiologic Effects of Smoking on the Skin

Tobacco smoke contains a complex mixture of gaseous and particulate compounds, several of which may have the potential to exert physiologic and pharmacologic impacts. Nicotine has for decades been regarded as a primary factor that engenders smoking-related disorders, but recent evidence clearly demonstrates that its temporary vasoactive effect on the skin and subcutaneous perfusion cannot satisfactorily explain the pathophysiologic mechanisms that impair wound healing and contribute to smoking-related disorders.[1]

Smoking produces systemic immunomodulatory effects through the release of reactive oxygen species from tobacco smoke, which is believed to cause a cascade of detrimental effects on normal inflammatory cell function by attenuating phagocytosis and bactericidal mechanisms, as well as by increasing the release of proteolytic enzymes.[2,3] In addition, collagen synthesis and the deposition of mature collagen in the extracellular matrix are reduced through smoking.[4] Such disruptive influences on these biologic mechanisms culminate in adverse affects on the cellular reparative pathways of the skin and its appendages, which can be observed in the healing of acute wounds in smokers. This cohort has a significantly higher risk of post-operative dehiscence and infection, and in patients who are heavy smokers, slowed or arrested healing of chronic wounds can also occur.[5]

Undoubtedly, degenerative skin disorders are the result of smoking-induced defects in reparative mechanisms and the progression of extracellular degradation of elastin, collagen, and other extracellular matrix molecules. More complex, and in fact unknown, is the role of smoking in the etiology of autoimmune and neoplastic skin diseases. It is increasingly apparent that the immunomodulatory effects and alteration of inflammatory cell function from smoking influences the clinical course of cutaneous diseases. Dermatologic research still needs to elucidate why smoking is an aggravating factor for some diseases, while appearing to mitigate the clinical course of others.

Visible Effects of Tobacco Smoking

Model[6] described the following as common features of a smoker's face: lines or wrinkles on the face, typically radiating at right angles from the upper and lower lips or corners of the eyes, deep lines on the cheeks, or numerous shallow lines on the cheeks and lower jaw; a subtle gauntness of the facial features with prominence of the underlying bony contours; an atrophic, slightly pigmented grey appearance of the skin; and a plethoric, slightly orange, purple, and red complexion. These findings were shown to be independent of age, social class, exposure to sunlight, and recent change in weight. An additional feature that is sometimes present is large open and closed comedones with furrows and nodules in the periorbital area characteristic of Favre-Racouchot syndrome (smoker's comedones).[7] The nails of smokers may show a yellow discoloration, and in heavy smokers who suddenly cease smoking (e.g., due to an abrupt illness), a sharp demarcation line develops between the yellow nail plate and the newly developed proximal pink nail (referred to as Harlequin nail or quitter's nail).[8] Yellow discoloration of the hair and beard can also be seen in smokers, particularly in gray-haired individuals (e.g., smoker's moustache). Furthermore, smoking has been linked to premature graying and loss of hair, although the supporting evidence remains circumstantial. Non-malignant changes in the oral mucosa of smokers are common and include gingival pigmentation (smoker's melanosis), leukoplakia of the tongue (smoker's tongue), and a gray-white keratinized palate with multiple red umbilicated papules that represent inflamed salivary glands (smoker's palate/nicotine stomatitis).[9]

Smoking as an Etiological Factor in Skin Diseases

Smoking has been implicated as a causal or influencing factor for certain dermatologic disorders (Table 1). The obvious detrimental effects from smoking preclude experimental prospective interventions on human subjects, and therefore, the main body of evidence for these associations is derived from case-control studies. However, because of inherent biases connected with this type of research, as well as with cohort and observational studies, the conclusions that can be drawn from their findings are limited.

Systemic Lupus Erythematosus

There is fairly good evidence to support a causal link between tobacco smoking and systemic lupus erythematosus (SLE), as it has been demonstrated that anti-malarial therapeutic agents for lupus are less effective in smokers.[10] A meta-analysis of seven case-control studies and two cohort studies found a 1.5 times increased risk of SLE in current smokers, when compared with non-smokers. The finding remained significant after adjustment for age, sex, race, alcohol consumption, and socioeconomic status.[11] However, the result may have been affected by publication bias due to an absence of studies reporting negative findings. Furthermore, former smoking was not found to be a risk factor for SLE. Exposure to smoking in early childhood or *in utero* was not associated with onset of SLE in a prospective cohort study.[12] Discoid lupus erythematosus (DLE) has also been linked to smoking in several case-control studies, which have shown consistently higher smoking rates in DLE patients.[13]

Psoriasis

Smoking has been observed to be a strikingly common current or former habit among patients with palmoplantar pustulosis (PPP) at the time of diagnosis. In fact, up to 95% of patients with PPP were smokers in a case series study.[14] In addition, psoriasis appears to be closely linked to smoking. Tobacco smoking has not only been shown to exacerbate preexisting psoriasis, but usage has also been frequently found among individuals with new-onset disease. Furthermore, smoking has been shown to increase the risk of psoriasis in a dose-dependent manner and to drive disease severity.[15] Moreover, a large population-based study in Sweden of 9773 patients with a hospital discharge diagnosis of psoriasis reported an increased risk of tobacco-related cancers among psoriatic patients, but it is difficult to determine whether this observation reflects a higher frequency of smoking in this population or a shared adverse effect of smoking on psoriasis and cancer risk.[16]

Skin Cancer

The association between cutaneous squamous cell carcinoma (SCC) and smoking has been described in case-control and cohort studies. Notably, in the Nurses' Health Study, smokers had a 50% increased risk of incident SCC compared with non-smokers.[17] It has been speculated that this finding could be confounded by a higher exposure to UV-radiation among cigarette users. A large prospective study of Swedish men failed to replicate the positive association between SCC and smoking.[18] In a Finnish study involving 290 same-sex twin

Prevalence in Smokers	Skin Disease	Level of Evidence
Higher Prevalence	Basal cell carcinoma	Case-control
	Cutaneous squamous cell carcinoma	Prospective cohort and case-control
	Genital warts and HPV infection	Prospective cohort and case series
	Hidradenitis suppurativa	Case series
	Discoid lupus erythematosus	Case-control
	Systemic lupus erythematosus	Meta-analysis (case-control and cohort studies)
	Oral cancers	Prospective cohort and case-control
	Palmoplantar pustulosis	Case-control
	Psoriasis	Prospective cohort and case-control
Lower Prevalence	Aphthous ulcers	Case series
	Behçet's disease	Case series
	Herpes labialis	Cohort
	Kaposi's sarcoma in AIDS patients	Case-control
	Pemphigus vulgaris	Case-control
Conflicting Evidence	Acne	Cohort and case-control
	Hand eczema	Cohort
	Melanoma	Case-control

Table 1. Evidence of skin diseases associated with smoking

pairs, where a single twin was diagnosed with basal cell carcinoma (BCC), significantly greater risk was observed to be related to smoking status in females but not in males.[19] Moreover, smoking has been linked to BCC of the eyelid in women but not in men. A convincing link has not been established with cutaneous malignant melanoma (MM). In fact, several large case-control studies have found no association between tobacco smoking and MM. Although one study of stage-I melanoma patients found some evidence of thicker lesions among smokers, whereas two other studies demonstrated a lower risk of acral melanoma.[19] The risk of oral cancers is increased in smokers and different researchers have consistently corroborated this finding.[20]

Hidradenitis Suppurativa

Observational studies have found a much higher prevalence of smoking (up to 90%) among patients with hidradenitis suppurativa, whereas smoking cessation did not appear to alter disease activity.[21] Smokers also had a higher (dose-dependent) prevalence and severity of acne compared with non-smokers in a large German population study; this effect was independent of age, sex, and socioeconomic status. On the contrary, two smaller case-control studies found a lower than expected prevalence of acne among smokers.[22]

Other Skin Diseases

A few other skin disorders have been infrequently associated with smoking. For example, hand eczema was more prevalent in smokers compared with non-smokers in a large cross-sectional study of the general population.[23] Moreover, genital warts and human papillomavirus infections were more common among individuals who smoke cigarettes.[24] Crohn's disease is more prevalent and severe in smokers, but smoking has not been examined in relation to cutaneous metastatic Crohn's disease.[22]

In contrast, ulcerative colitis (UC) is less frequent in smokers, and as such, smoking may confer a beneficial effect on the course and severity of UC. Accordingly, treatment with topical or systemic nicotine has been hypothesized to be beneficial in pyoderma gangrenosum, which is often associated with UC.[22] Smoking has been shown to be protective for several other mucocutaneous disorders, probably due in part to nicotine's anti-inflammatory properties. In particular, some studies have found that patients with pemphigus vulgaris were less likely to have a positive history of smoking when compared with the control group, and smoking may improve the clinical course of the disease.[25] Also, recurrent herpes labialis and classical Kaposi's sarcoma are less common in smokers.[26,27] In addition, smoking may have beneficial effects on aphthous ulcers (e.g., prevent the development of new aphthae), and in Behçet's disease, patients who cease smoking can experience a greater risk of recurrent ulcers.[28]

Conclusion

Tobacco smoking induces oxidative stress, which has immunomodulatory effects by changing inflammatory cell function and releasing proteolytic enzymes; the latter alters connective tissue turnover and degrades skin connective tissue. From the literature, it is reasonable to presume an etiological role for tobacco smoking in certain dermatologic conditions, particularly SLE, psoriasis, PPP, cutaneous SCC, hidradenitis suppurativa, and genital warts. In other skin disorders, smoking appears to mitigate the clinical course, notably in pemphigus vulgaris, pyoderma gangrenosum, aphthous ulcers, and Behçet's disease. The pathophysiology, etiology, and clinical course of these skin diseases appear to be related to the immunomodulatory effects of smoking, but further studies are needed to identify and elucidate the specific mechanisms at work.

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Update on Drugs

Name/Company	Approval Dates/Comments
CD56-binding monoclonal antibody (huN901) + maytansinoid cytotoxic agent (DM1) *IMGN901* ImmunoGen, Inc.	The US FDA granted orphan drug designation in March 2010 to the IMGN901 compound (an antibody-drug conjugate) for the treatment of Merkel cell carcinoma (MCC). Through a separate process, the European Union's Committee for Orphan Medicinal Products (COMP) also granted IMGN901 orphan medicinal product designation for the treatment of MCC. IMGN901 binds with high affinity to CD56 expressed on the surface of tumor cells. Once bound, the conjugate is internalized and the antimitotic agent (DM1) is released.
Small molecule oxychlorine compound *Microcyn® Skin and Wound HydroGel* Oculus Innovative Sciences	The US FDA granted clearance for new dermatology indications in March 2010 to Microcyn® Skin and Wound HydroGel. This prescription product is intended for use, under the supervision of a healthcare professional, in the management of wounds, including itch and pain relief associated with skin irritation, sores, injuries, and ulcers of dermal tissue.
Antifungal agent *K101/Kaprolac®* Moberg Derma AB (Sweden) Medical Futures Inc. (Canada)	In April 2010, marketing authorization in the European Union was granted to this non-prescription topical solution for the treatment of discolored and damaged nails (e.g., caused by onychomycosis or nail psoriasis). Application is once-daily on affected nails and improvements can be seen within 2-4 weeks of treatment. The product is based on the Kaprolac® principle, which is a patented composition of well-known dermatologic compounds.

Drug News

In April 2010, Bayer HealthCare announced that it has changed the labeling information for Yaz® and Yasmin® (drospirenone + ethinyl estradiol) to state that the risks of venous thrombosis associated with the drugs are similar to those reported with other oral contraceptives. The label changes were coordinated with the US FDA and are based on data gathered from studies involving over 120,000 women. A similar amendment took place in the European Union for an updated label of Yasmin® to reflect a similar risk profile.

In April 2010, the US FDA announced that it is reviewing the safety of triclosan. In an online consumer update, the agency advised it is investigating recent studies that demonstrate repeated heavy use of this chemical can alter hormone regulation in some animals. Other studies suggest the chemical promotes bacterial resistance to antibiotics (e.g., methicillin-resistant *Staphylococcus aureus*). The FDA currently has no evidence that triclosan is hazardous to humans and is not recommending consumer avoidance. However, the agency states that there is an absence of data supporting triclosan-containing products are more effective than soaps without this antimicrobial agent. Earlier this year, the European Union instituted a ban on triclosan from any products that may come into contact with food. More information is available at: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm205999.htm.