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A world of hyperpigmentary disorders

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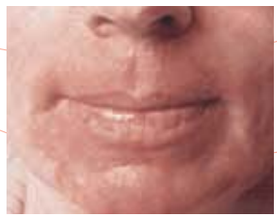
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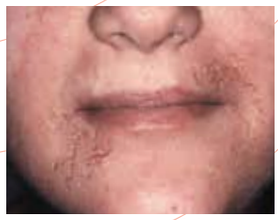
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A world of hyperpigmentary disorders

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Normal and abnormal skin color

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KEYWORDS
Hyperpigmentation;
Skin Color;
Melanin;
Melanosomes;
Melanocytes

Summary
The varieties of normal skin color in humans range from people of «no color» (pale white) to «people of color» (light brown, dark brown, and black).
Skin color is a blend resulting from the skin chromophores red (oxyhaemoglobin), blue (deoxygenated haemoglobin), yellow-orange (carotene, an exogenous pigment), and brown (melanin). Melanin, however, is the major component of skin color ; it is the presence or absence of melanin in the melanosomes in melanocytes and melanin in keratinocytes that is responsible for epidermal pigmentation, and the presence of melanin in macrophages or melanocytes in the dermis that is responsible for dermal pigmentation.
Two groups of pigmentary disorders are commonly distinguished: the disorders of the quantitative and qualitative distribution of normal pigment and the abnormal presence of exogenous or endogenous pigments in the skin. The first group includes hyperpigmentations, which clinically manifest by darkening of the skin color, and leukodermia, which is characterized by lightening of the skin. Hypermelanosis corresponds to an overload of melanin or an abnormal distribution of melanin in the skin. Depending on the color, melanodermia (brown/black) and ceruloderma (blue/grey) are distinguished. Melanodermia correspond to epidermal hypermelanocytosis (an increased number of melanocytes) or epidermal hypermelanosis (an increase in the quantity of melanin in the epidermis with no modification of the number of melanocytes). Ceruloderma corresponds to dermal hypermelanocytosis (abnormal presence in the dermis of cells synthesizing melanins) ; leakage in the dermis of epidermal melanin also exists, a form of dermal hypermelanosis called pigmentary incontinence. Finally, dyschromia can be related to the abnormal presence in the skin of a pigment of exogenous or endogenous origin.

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MOTS CLÉS
Hyperpigmentation ;
Couleur de la peau ;
Mélanine ;
Mélanosomes ;
Mélanocytes

Résumé
La couleur de la peau humaine va de la peau pâle ou blanche jusqu'à la peau colorée (brun léger, brun marron et noir). Elle résulte d'un mélange des chromophores rouges (oxyhémoglobine), bleus (hémoglobine désoxygénée), jaune-orangé (carotène, un pigment exogène) et bruns (mélanine). La mélanine est un constituant majeur de la couleur de la peau. La présence ou l'absence de mélanine dans les mélanosomes des mélanocytes et dans les kératinocytes sont responsables de la pigmentation épidermique, tandis que la mélanine dans les macrophages et les mélanocytes du derme est responsable de la pigmentation dans le derme. Parmi les anomalies pigmentaires, deux groupes sont individualisés : les anomalies quantitatives ou qualitatives de répartition d'un pigment normal et la présence anormale dans la peau de pigments exogènes ou endogènes. Le premier groupe comprend les hyperpigmentations qui se traduisent cliniquement par des assombrissements de la couleur de la peau et les leucodermies qui se caractérisent par un éclaircissement. Le deuxième groupe comprend des affections avec une coloration inhabituelle du tégument. Les hypermélanoses correspondent à une surcharge mélanique ou à une répartition anormale de la mélanine dans la peau. En fonction de la couleur on individualise les mélanodermies (brun/noir) et les cérulodermies (bleu/gris). Les mélanodermies peuvent correspondre à des hypermélanocytoses épidermiques (augmentation du nombre de mélanocytes) ou à des hypermélaninoses épidermiques (augmentation de la quantité de mélanine dans l'épiderme, sans que le nombre de mélanocytes soit modifié). Les cérulodermies peuvent correspondre à des hypermélanocytoses dermiques (présence anormale dans le derme de cellules synthétisant les mélanines). Il peut s'agir également d'hypermélaninoses dermiques, où il existe une fuite dans le derme de la mélanine épidermique (incontinence pigmentaire). Enfin une dyschromie peut être liée à la présence anormale dans la peau d'un pigment d'origine exogène ou endogène.

Introduction

Normal skin color varies from white to pink, and to yellow, brown, and black. In the different ethnic groups, there are pronounced variations in skin, head hair, and body hair. Several pigments, normally present in the skin, confer normal and abnormal skin colors: brown color is produced by melanins coming from melanocytes, the colors red and blue are produced by oxyhemoglobin and deoxyhemoglobin, and yellow comes from carotenes. These different variations can be combined. Melanins play the main role (Fig. 1), whether eumelanins or pheomelanins (colors varying from yellow to brown and black). The DHICA-eumelanins (5,6-dihydroxyindole-2-carboxylic acid) are the brown melanins and the DHI-eumelanins (5,6-dihydroxyindole) are the black melanins. Reduced hemoglobin and oxidized hemoglobulin and carotene are, respectively, pinkish and yellowish-orange. Hyperpigmentation disorders generally result from an increased production of melanin and sometimes from a density of highly active melanocytes. Anomalies in skin coloration can also be caused by deposits of substances such as medicines or heavy metals (iron, etc.) in the dermis.

The number of melanocytes in Caucasian and Black skin is similar; however, the number and size of melanosomes are greater in pigmented epidermis.

Figure 1. Normal human epidermis.

Classifications of skin color and melanin and non-melanin pigmentation abnormalities

There are three categories of pigmentation abnormalities: hypomelanosis, hyperpigmentations caused by accumulation of or a disorder of the distribution of normal pigment in the skin, and hyperpigmentations resulting from the abnormal presence in the skin of a pigment, originating either exogenously or endogenously. Hypomelanosis and leukodermia will not be detailed in this study. Hyperpigmentation disorders can be called hypermelanosis when the number of melanocytes is normal but the quantity of melanin is increased (Addison disease, melasma) or hypermelanocytosis when the number of melanocytes is increased (Ota nevus). The objective of this classification is to characterize the pigment disorders according to the increase or decrease of melanin or melanocytes.

Certain diseases are characterized by the association or epidermal and dermal hyperpigmentation (mixed hypermelanosis) or by leukomelanoderma (hypo- and hyperpigmentation).

Hyperpigmentations caused by accumulation of or a disorder of the distribution of normal pigment in the skin

Brown hypermelanosis

Brown skin results directly from the absorption spectrum of epidermal eumelanins. Visible light is absorbed by the melanins in the epidermis. Black skin absorbs a great deal of light and appears brown or black. Excess melanin in brown hypermelanosis can result from the increased production of melanin with a) an increased number of melanocytes or b) a normal number of melanocytes. These anomalies can result from genetic or acquired factors.

Epidermal melanocytic hypermelanosis

These lesions are characterized by a great number of epidermal melanocytes that produce excessive quantities of melanins in the epidermis (Fig. 2). Lentigines are prototypes of epidermal melanocytic hypermelanosis accompanied by epidermal hyperplasia (Fig. 3). The morphology is also hyperplasic, because histologically there is a high number of melanocytes that produce an excessive quantity of melanin in the epidermis and a lengthening of the rete ridges.

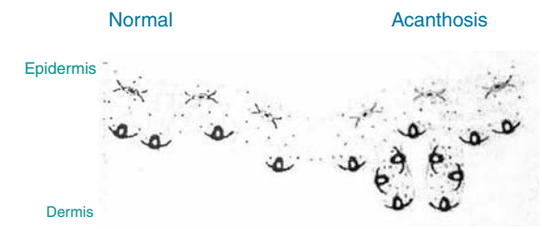
Epidermal melanotic hypermelanosis

In these lesions, the number of epidermal melanocytes is normal. Hypermelanosis results from an increase in secondary epidermal melanins because of their deterioration and/or elimination. Café-au-lait spots and freckles are typical examples of melanotic epidermal hypermelanosis (Figs. 4 and 5).

Ceruloderma

Blue skin or ceruloderma is due to the optical effects related to melanins or other black substances in the dermis. Normally, the dermis has no melanin and appears yellow, white, or pink depending on the quantity of blood present. Dermal melanin has a wide absorption spectrum. It absorbs incident visible light by two mechanisms: it absorbs incident light based on a mean mathematical coefficient for each wave length in the tissues. Long wave lengths such as those in the red region (600–700 nm) are more absorbed than the shorter ones corresponding to the blues, the region ranging from 400 to 500 nm. Therefore, the low reflectance of light in a red wave length gives dermal melanin a blue appearance. Thus, the color blue of the lesion is not derived from the spectral reflectance increased in the blue region, but from the reduced spectral reflectance of the red region.

Blue hypermelanosis or ceruloderma can result from three different mechanisms: a) dermal melanotic or pigmentary incontinence, i.e., melanin formed in the epidermis



Hyperpigmented skin has elongations of the rete ridges, a process called acanthosis. In this situation, the epidermis has a high number of melanocytes that have produced an excessive quantity of melanins. There is no pigment in the dermis. A drawing of normal skin is presented for comparison.

Figure 2. Epidermal melanocytosis.

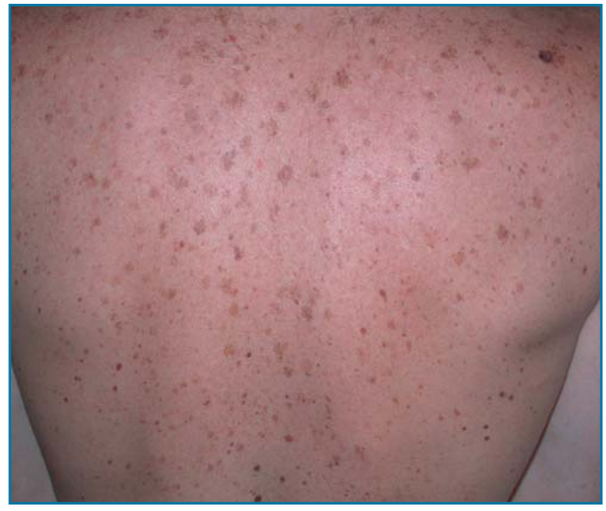
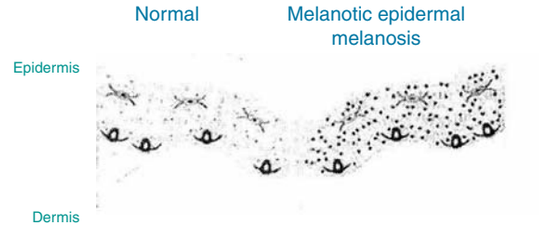


Figure 3. Multiple solar lentigines on the upper back and shoulders (sun spots, a marker of melanoma).



Hyperpigmented skin is caused by excessive quantities of melanins but a normal number of melanocytes. Clinical examples are ephelides, café-au-lait spots, and pigmentary urticaria. A drawing of normal skin is presented in comparison.

Figure 4. Melanotic epidermal melanosis.

Figure 5. Ephelides.

by epidermal melanocytes and transferred to the dermis; b) dermal melanocytic hyperpigmentation, i.e., melanin formed by dermal melanocytes; and c) non-melanic dermal pigmentation attributed to pigments other than melanin deposited in the dermis.

Dermal hypermelanosis

Melanins can accumulate in the dermis, the melanophages, and the melanophagolysosomes. This transfer of melanosomes from the epidermal cells to the dermis is called pigmentary incontinence. This process is frequent, notably in inflammatory dermatosis causing damage to the basal cells of the epidermis or the dermoepidermal junction (Figs. 6 and 7).

Dermal melanocytosis

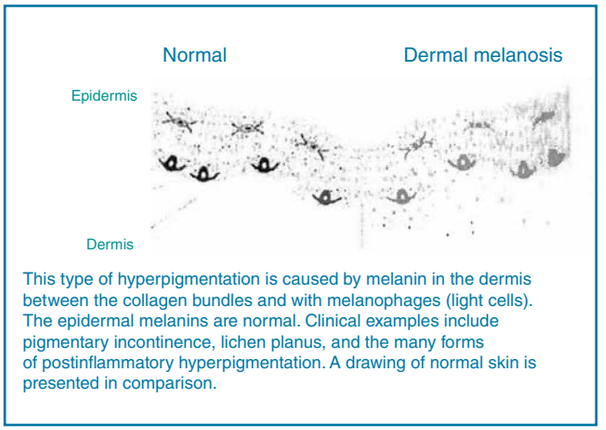
The melanocytes that are abnormally present in the dermis can synthesize melanins. These pigmentary cells are surrounded by the structure of the basement membrane and do not transfer their melanosomes to the keratinocytes and to dermal cells. (Fig. 8). This process is called dermal melanocytosis. Ota's nevus (Fig. 9), Ito's nevus, and acquired blue facial macules are examples. The most important mechanisms involved in pigmentary incontinence are interactions between the macrophages and the keratinocytes called Civatte bodies, which contain melanosomes.

Hemic hyperchromia

In addition to melanins, the blood located in the superficial capillaries of the dermal plexus contributes to normal skin color. Cyanosis resulting from decreased local accumulation of hemoglobin is one variety of hyperchromia. Red and brown skin colors can also stem from deposits of hemosiderin in the dermis following various types of vascular lesions.

Thickening of the epidermis

Dark skin results from alterations in the epidermis and the stratum corneum as in ichthyosis, seborrheic keratosis, etc. The skin color results from the thickness of the epidermis, the stratum corneum, and the rupture of the translucence of the stratum corneum. The column of melanin is thick and the quantity of light absorbed is high (Figs. 11 and 12).



This type of hyperpigmentation is caused by melanin in the dermis between the collagen bundles and with melanophages (light cells). The epidermal melanins are normal. Clinical examples include pigmentary incontinence, lichen planus, and the many forms of postinflammatory hyperpigmentation. A drawing of normal skin is presented in comparison.

Figure 6. Dermal melanosis.

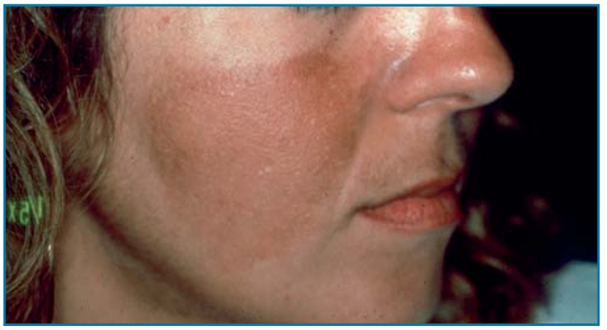
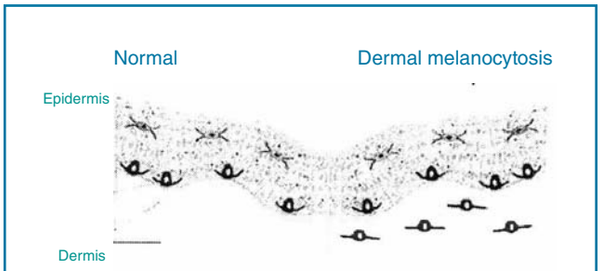


Figure 7. Postinflammatory hyperpigmentation.



This type of hyperpigmentation is caused by localized ectopic melanocytes in the dermis. The epidermal melanin is normal. This lesion is blue or blue-grey in color. The clinical examples are Ota nevus and Ito nevus. A drawing of normal skin is presented in comparison.

Figure 8. Dermal melanocytosis.

Non-melanic dermal pigmentation: disorders related to exogenous and endogenous pigments

Many medications or the accumulation of pigments such as porphyrin can induce brown hypermelanosis through different mechanisms, notably photosensitivity and the direct stimulation of the melanogenic activity of melanocytes.

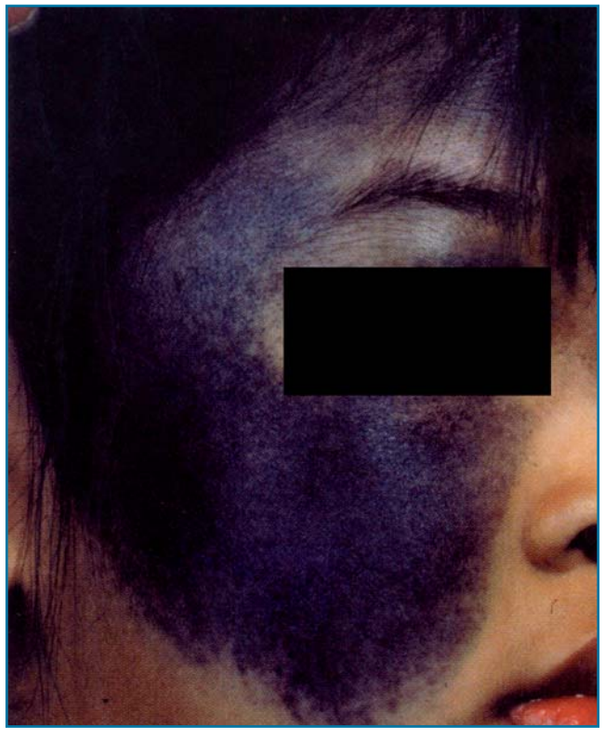


Figure 9. Ota's nevus.

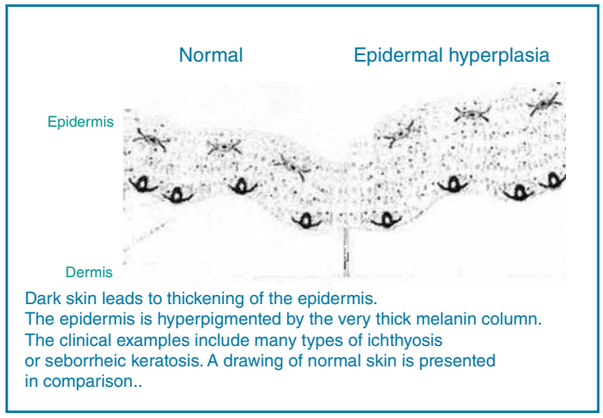


Figure 10. Thickening of the epidermis.

A number of chemical and pharmacological agents can be present in dermal pigmentation. Drugs, heavy metals, and other exogenous agents can deposit in the dermis and give blue-grey pigmentations miming dermal melanosis. These

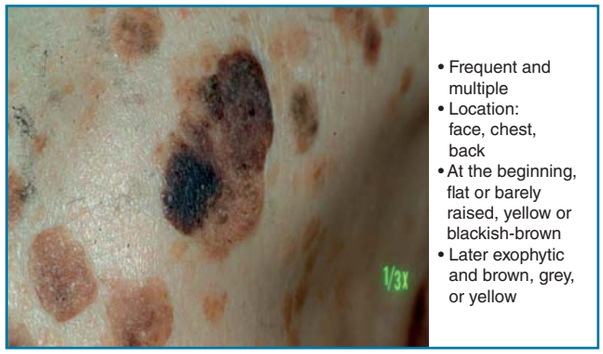


Figure 11. Flat seborrheic keratosis.

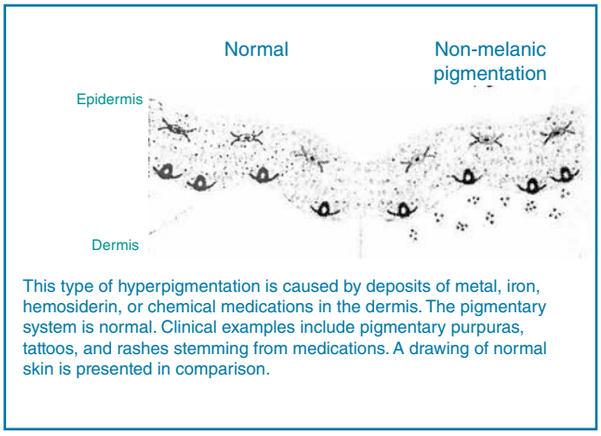


Figure 12. Hyperpigmentation caused by exogenous and endogenous products.

drugs are minocycline, hydroquinone, and antimalarials. The heavy metals are mercury, silver, gold, bismuth, arsenic, and lead. Ochronosis also gives a similar pigmentation.

Conflicts of interests

J.- P. Ortonne: none.

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Pigmentary lesions in patients with increased DNA damage due to defective DNA repair

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KEYWORDS
Pigmentary lesions;
Ultraviolet radiation (UV);
DNA damage;
Xeroderma pigmentosum (XP)

Summary
The occurrence of abnormally pigmented skin lesions is a common phenomenon and often associated with the influence of ultraviolet radiation (UV) and other sources of DNA damage. Pigmentary lesions induced by UV radiation and other sources of DNA damage occur in healthy individuals, but human diseases with defective DNA repair represent important models which allow the investigation of possible underlying molecular mechanisms leading to hypo- and hyperpigmentations. There are several hereditary diseases which are known to go along with genetic defects of DNA repair mechanisms comprising Xeroderma pigmentosum (XP), Cockayne syndrome (CS), Trichothiodystrophy (TTD), Werner syndrome (WS), Bloom syndrome (BS), Fanconi anemia (FA) and Ataxia telangiectasia (AT). These diseases share clinical characteristics including poikilodermatic skin changes such as hypo- and hyperpigmentation. Since UV radiation is the most common source of DNA damage which can cause pigmentary lesions both in healthy individuals and in patients with genetic deficiency in DNA repair, in the present article, we focus on pigmentary lesions in patients with XP as an example of a disease associated with genetic defects in DNA repair.

MOTS CLÉS
Lésions pigmentaires ;
Exposition aux UV ;
Altérations de l'ADN ;
Xeroderma pigmentosum (XP)

Résumé
L'induction d'anomalies pigmentaires est très commune et résulte principalement de l'exposition aux UV mais aussi à d'autres sources d'altérations de l'ADN. Les lésions pigmentaires ainsi induites peuvent survenir chez des patients sains, mais les maladies de réparation de l'ADN peuvent être considérées comme un modèle d'étude des mécanismes moléculaires des hypopigmentations et des hyperpigmentations. Il existe de nombreuses maladies génétiques qui comprennent des anomalies de réparation de l'ADN, notamment le xeroderma pigmentosum (XP), le syndrome de Cockayne (SC), la trichothiodystrophie (TTD), le syndrome de Werner (SW), le syndrome de Bloom (SB), l'anémie de Fanconi (AF) et l'ataxie télangiectasie (AT). Toutes ces maladies ont des éléments cliniques communs,

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notamment un état poïkilodermique comprenant des troubles pigmentaires. L'exposition aux UV étant le principal inducteur d'altérations de l'ADN et d'anomalies pigmentaires chez les sujets sains comme chez ceux atteints d'anomalies de réparation de l'ADN, cet article sera centré sur les lésions pigmentaires du XP, cette maladie étant l'archétype des défauts génétiques de réparation de l'ADN.

Introduction

The occurrence of abnormally pigmented skin lesions is among the most frequent phenomena observed in clinical dermatology. Importantly, pigmentary changes are often directly caused by sources of DNA damage such as ultraviolet radiation (UV) but also laser treatment, exposure to X-ray radiation as well as chemicals [1-3]. Therefore, in this article we will describe the quality, pathogenesis and etiology of pigmented lesions with a focus on patients with genodermatoses such as Xeroderma pigmentosum (XP).

Pigmentary lesions induced by UV radiation

Pigmentary lesions induced by UV radiation include benign tumors of the skin such as melanocytic naevi and ephelides as well as tumors of the skin such as pigmented basal cell carcinoma, precursor lesions such as lentigo maligna or pigmented solar keratoses. The development of melanoma is of very high importance in this context due to the high mortality of this tumor and particularly for this tumor the causative role of UV radiation has been shown within the last years [4,5].

Clinically, the term melanocytic naevus is often used as an umbrella term for the different entities such as solar lentigo, lentigo simplex, mucosal lentigo, Spitz naevus, blue naevus and dermal melanocytosis. The exact clinical description will be given elsewhere but unlike melanocytic naevi, ephelides have to be regarded as completely different entities since they disappear completely during winter time and present an increase of melanin in the basal cells of the epidermis without an elevated number of melanocytes [6,7].

Pigmentary lesions induced by other sources of DNA damage

Pigmentary lesions of the skin induced by UV radiation and other sources of DNA damage occur in healthy individuals, but they are more frequent in patients with genetic defects in DNA repair mechanisms already indicating the central role of DNA damage and its repair in the development of pigmentary changes. UV radiations are the most common source of DNA damage which can cause pigmentary lesions both in healthy individuals and in patients with genetic deficiency in DNA repair. Other sources of DNA damage with clinical relevance, which can also result in pigment changes, comprise laser, X-ray radiation and chemicals (e.g. carcinogens in cigarette smoke, alkylating or DNA-cross-linking agents).

Exposure to X-rays can cause the prototype of an acquired poikiloderma with cutaneous atrophy, hypo- and hyperpigmentation as well telangiectasia [1-3].

Hereditary diseases with defects in DNA repair

The human genome is continuously exposed to different sources of DNA damage such as UV radiation, X-ray radiation, chemicals and laser. The human organism therefore commands a system of highly conserved and effective DNA repair mechanisms such as nucleotide excision repair (NER), double strand break repair, base excision repair and mismatch repair. Defects in these repair mechanisms may result in DNA damage induced by UV radiation and other sources of DNA damage due to genetic instability [1, 8-11].

There are several hereditary diseases which are known to go along with genetic defects of DNA repair mechanisms comprising XP, Cockayne syndrome (CS), Trichothiodystrophy (TTD), Werner syndrome (WS), Bloom syndrome (BS), Fanconi anemia (FA) and Ataxia telangiectasia (AT). Interestingly, these diseases with defects in very different DNA repair mechanisms share clinical characteristics such as growth retardation, neurological symptoms, premature aging and skin alterations. Particularly, among the dermatologic symptoms we find development of telangiectasia, dry skin (xerosis), pathological wound healing, an increased risk of developing malignant skin tumors and practically all of these diseases show pathological changes of their skin pigmentation [1, 8-11]. This readily illustrates the important role of all types of DNA damage as well as the different mechanisms of DNA repair. Thus, human diseases with defects in DNA repair not only represent important models to investigate the underlying causes but also to develop therapeutic strategies against abnormal pigmentation.

Xeroderma pigmentosum

XP is a rare autosomal recessive inherited disease with a prevalence of 1: 1,000,000 in the US and Europe and up

to 1: 100,000 in Northern Africa [12]. XP, as well as CS and TTD, are caused by defects in the repair mechanism NER. One of the central functions of this repair system is the repair of DNA damage induced by UV radiation. In addition to UV-induced DNA damage, the NER system also plays an important role in the repair of bulky damage, which can be caused by chemicals such as carcinogens in cigarette smoke, by alkylating or DNA-cross-linking agents, thus readily indicating the importance of this repair mechanism in the protection from many of the adverse agents involved in causing pigmentary skin changes.

There are seven XP complementation groups (XP-A to -G), each with a distinctive deficient in NER [1]. Each complementation group corresponds to a certain gene whose product is involved in the repair of UV- or chemical-induced damage in DNA. Another variant form with normal NER but a deficiency in DNA polymerase η is known (designated XP variant). This polymerase is required to replicate DNA containing unrepaired damage.

Clinical features of XP comprise extreme sensitivity to sunlight, resulting in sunburn, an approximately 1000-fold increased risk of developing skin cancer and a minority of patients show progressive neurological abnormalities. Importantly, the first symptoms often manifest in early childhood and comprise pigmentary changes which are the first signs of this diagnosis. The first skin changes are most frequently abnormal lentigines on sun-exposed areas. Abnormal lentiginosis is often followed by the typical appearance of poikiloderma with hypo- and hyperpigmentation, atrophy and telangiectasia and finally skin aging and the development of multiple skin cancers. Among skin cancers in XP patients, basal cell carcinoma and squamous cell carcinoma are most frequent, but melanoma can also appear [1, 13].

Pigmentary lesions in patients with XP and other hereditary diseases

Xeroderma pigmentosum

Pigmentary lesions induced by UV radiation and other sources of DNA damage such as chemicals (e.g. carcinogens in cigarette smoke, alkylating or DNA-cross-linking agents) are often found in patients with XP. As described above, abnormal lentiginosis in patients with XP occurs predominantly on sun-exposed areas and unusually early compared to healthy individuals with an onset often in the first year of life. This fact underlines the central role of NER in the repair of UV-induced DNA damage. Abnormal lentiginosis in patients suffering from XP presents as a freckle-like pigmentation due to an increased number of melanocytes (Figs. 1 and 2).

These unusual early pigmentation changes in sun-exposed areas can help to distinguish XP from other genodermatoses such as CS and TTD and from other diseases associated with lentigines such as Peutz-Jeghers-syndrome, Leopard syndrome, dyschromatosis universalis hereditaria and Carney complex, in which the pigmentation is not sun-associated. Another feature which distinguishes XP from diseases like Leopard syndrome and Carney complex is the fact that pigmentation in these diseases is more uniform and that there is a lack of hypopigmentation and telangiectasia [1, 13].

Other diseases with pigmentary changes

In patients with AT hyperpigmentation can also occur along with several other characteristic symptoms but compared to patients with XP it is not freckled but diffuse.

Furthermore, most of the patients with premature aging syndromes such as WS show poikilodermatous features besides other typical symptoms. Typical symptoms in WS patients are normal development for the first decade, hyperkeratosis over bony prominences, high-pitched voice, early development of diabetes, atherosclerosis and large slow-to-heal ulcers, features which help to distinguish XP from WS.

In patients with progeria the development of hypo- and hyperpigmentation in sun-exposed areas is also a characteristic feature but there are a lot of other characteristics such as a large skull, frontal bossing, bulging eyes, beaked nose, small chin, lacking of scalp, eyelid and eyebrow hair, osteoporosis and premature atherosclerosis, which are not found in patients with XP.

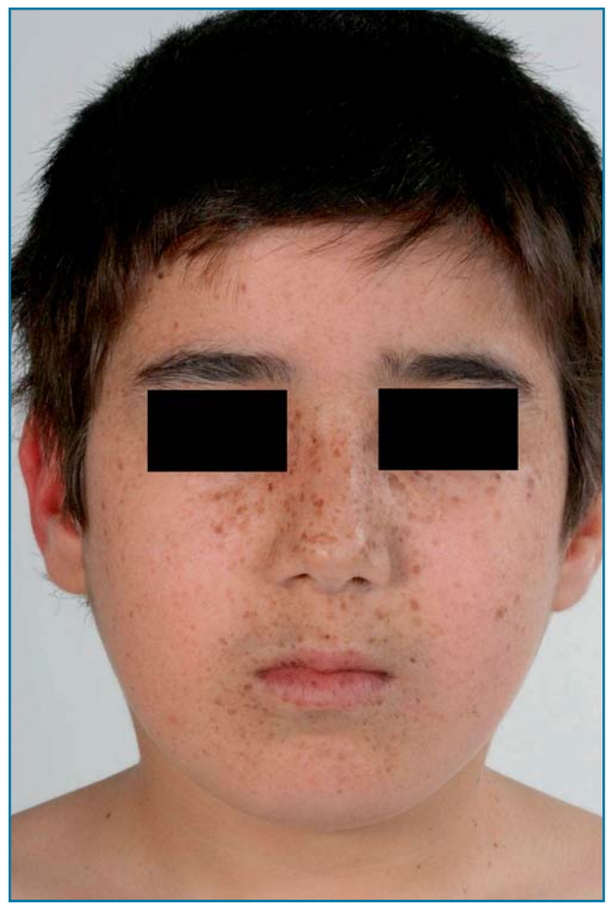

Figure 1. Clinical image of a seven year old boy suffering from XP presenting with mild freckling.

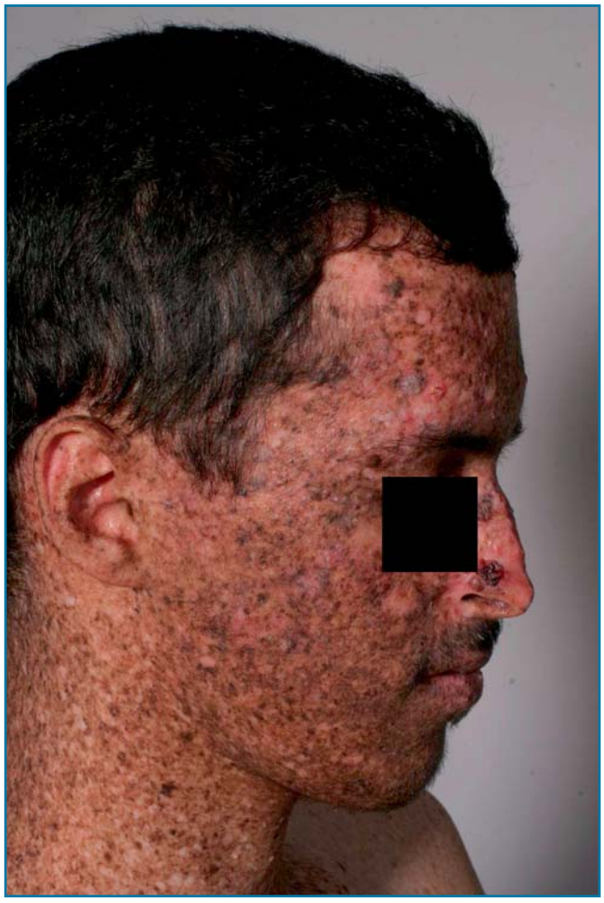

Figure 2. Clinical image of a 29 year old man with XP. Multiple basal cell carcinomas and squamous cell carcinomas as well as hypo- and hyperpigmentation in sun-exposed skin.

In patients with dyskeratosis congenita, poikiloderma is a typical feature but unlike in patients with XP the hyperpigmentation in patients with dyskeratosis congenita is reticulated, dusky and of a grayish color [1].

In patients with FA the hyperpigmentation is diffuse compared to the freckle-like hyperpigmentation in patients with XP.

As described above, X-ray radiation can cause poikiloderma with hyper- and hypopigmentation in healthy individuals. Although patients with XP are much more susceptible to UV-induced tumors and pigmentary lesions than healthy individuals, the skin reaction of XP patients to X-ray radiation is usually not abnormal [1].

Pigmentary lesions in acquired diseases

Pigmentary lesions may also result from acquired diseases which can go along with poikiloderma such as connective tissue disorders and cutaneous lymphomas (e.g. poikilodermatic mycosis fungoides) [1].

Table 1 overviews different diseases with pigmentary changes.

Conclusion

Pigmentary lesions are among the most frequent lesion of human skin in our society. Diseases with defects in DNA repair show very early development of pigmentary changes of a wide clinical variety, which indicates the central role of DNA damage as well as its repair in the pathophysiology of pigmentary skin lesions. Interestingly, areas of hypo- and hyperpigmentation are exactly adjacent in UV-exposed skin of these diseases. Since the exact mechanisms for unwanted excessive hyperpigmentation are not fully elucidated, diseases with defective DNA repair are important models in the investigation of the development of pigmented skin lesions. And even more importantly, since the hypopigmented areas occur in close proximity to hyperpigmentation, the investigation of the underlying mechanisms will possibly also help to identify strategies of prevention as well as treatment of unwanted pigmentary changes.

As UV radiation is the most common source of DNA damage which can cause pigmentary lesions both in healthy individuals and in patients with genetic deficiency in DNA repair, sun protection measurements such as sun screen, UV-protective textiles and hats are currently the most important measures in the prevention of pigmentary skin lesions both in healthy individuals and in patients with genetic deficiency in DNA repair. Further research is necessary to develop safe and efficient strategies to prevent and even treat pathological pigmentary skin changes.

Conflicts of interest statement

L. Krieger: none

M. Berneburg: Clinical trials as main (head) clinical or laboratory investigator, or study coordinator (Galderma, La Roche Posay, Spirig); Clinical trials as co-investigator or study contributor (Galderma, La Roche Posay, Spirig); occasional involvements: expert reports ((Galderma, La Roche Posay, Spirig); occasional involvements: advisory services (Galderma, La Roche Posay, Spirig); conferences: attendance as contributor (Galderma, La Roche Posay, Spirig); conferences attendance as audience member (Galderma, La Roche Posay, Spirig).

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Table 1
Pigmentation in different diseases

	Xeroderma pigmentosum	Peutz-Jeghers syndrome	Leopard syndrome	Carney complex	Dyschromatosis universalis hereditaria	Ataxia telangiectasia	Werner syndrome	Progeria	Fanconi anemia
Characteristics of pigmentation	Early; freckled	Perioral, hands, feet, mucosa	Uniform	Uniform	Reticulated, dusky, grayish; Face, trunk, thighs	Diffuse, only occasional			Diffuse
Hypopigmentation	+	-	-	-	-	-	+	+	+
Telangiectasia	+	-	-	-	+	+	+	+	-
Sun-associated pigmentation	+	-	-	-	-	-	-	+	-
Inheritance	AR	AD	AD	AD	x-linked recessive	AR	AR	AD	AR

AR = autosomal recessive
AD = autosomal dominant

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Considerations on photoprotection and skin disorders

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KEYWORDS
Photoprotection;
Sunscreens;
Skin diseases;
Hyperpigmentation

Summary
Excessive exposure to solar or artificial sources of UV radiation is deleterious to the skin and can cause or worsen several diseases. Detrimental effects of UV radiation exert an important role in the development of skin cancers, cause alterations on the immune response, and act as a trigger or aggravating factor for pigmentary disorders. A group of measures, including education, change of habits, use of physical barriers and sunscreens constitutes a significant part of the treatment of many skin disorders and are valuable preventive tools. This article summarizes the relevant studies addressing these issues, emphasizing the many aspects of photoprotection.

MOTS CLÉS
Photoprotection ;
Ecrans solaires ;
Maladies cutanées ;
Hyperpigmentation

Résumé
L'exposition excessive aux UV d'origine solaire ou artificielle a des effets délétères sur la peau et peut entraîner ou aggraver un certain nombre de dermatoses. Les effets néfastes de l'exposition aux UV jouent un rôle majeur dans le développement des cancers cutanés, modifient la réponse immunitaire et déclenchent ou aggravent certaines maladies pigmentaires. Le traitement de nombreuses maladies cutanées comprend des mesures préventives vis-à-vis du soleil, telles que l'éducation, les modifications comportementales et la photoprotection vestimentaire ou par des écrans solaires. Les données principales sur la photoprotection et son utilité en dermatologie seront abordées dans cet article.

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Introduction

In addition of being a source of energy and food, the sun is essential for human health, controlling biochemical and metabolic processes, biological rythms and even psychological well-being.

Having a pale skin was considered, for many centuries, as a marker of social status. In the late '30s radical changes in lifestyle happened, and be tanned started to be correlated to wealth, success and glamour [1]. As a result, many diseases and pathological changes associated with excessive sun exposure became more prevalent [2].

Photoprotection Measures

Solar light is capable of inducing many effects. Depending on the intensity of exposure, ultraviolet radiation B (UVB) can be genotoxic, causing damage to cellular DNA, can increase oxidative stress and induce inflammation and immunosuppression [3]. Repeated exposures to UVA is also related to oxidative cellular damage (leading to DNA damage), alterations of dermal connective tissue (elastosis) and to epidermal and stratum corneum thickening [4]. All these factors are involved in the process of photoaging and in various stages of carcinogenesis [5]. Excessive doses of UVR can cause sunburn photoallergic and phototoxic reactions, increase the incidence and severity of infections, decrease vaccine effectiveness and induce eye diseases like cataracts [4,6].

The human body has natural barriers to the penetration of UVR. Scalp and body hair provide physical protection and the stratum corneum, sweat and sebum help block the solar radiation, absorbing and reflecting UV radiation and visible light [7]. The human intrinsic physiological defense mechanism is composed by melanin, the anti-free radical system and the natural DNA repair complex [8]. In spite of it, additional protection is always necessary, taking into consideration individual characteristics, such as skin type, and duration of sun exposure.

Physical photoprotection

The use of protective clothes is an effective approach against the harmful effects of UV radiation. Color, thickness and weight of the fabric influence the photoprotection ability that is measured by the ultraviolet protection factor (UPF) [9]. This index represents the protection against both UVA and UVB radiation and, by determination of the European Committee for Standardization, its value must be greater than 40. Other accessories such as gloves, caps, hats and sunglasses are also important defensive measures [10].

Sunscreens

Sunscreens are substances which, when incorporated in suitable formulations, reduce the effects of UVR on the skin by absorption, reflection or scattering of the incident light [5].

The concept of SPF (Sun Protection Factor) was introduced in 1962 by Franz Greiter and, since then, has become the reference for measuring the efficacy of sunscreens [11]. The SPF indicates the ability of a given substance to protect against sunburn, mainly induced by UVB radiation. The UVA protection factor can be measured *in vivo* using the assessment of pigmentation as the Persistent Pigment Darkening (PPD) or by the photoxidative method of Immediate Pigmentation [6]. Recommendable sunscreens should provide consistent protection against UVB and UVA [11].

Many countries have specific legislation to better regulate photoprotection products. In Europe there are 26 UV filters registered by the European Cosmetic Directive (76/768/ECC); in the United States, 17 active sunscreens are approved by the FDA [5]. The minimal accepted SPF is 6, with the UVA protection being at least 1/3 of the SPF.

In the U.S., only sunscreens with an SPF value greater or equal to 15 are allowed to indicate that they help to reduce the risk of skin cancer and skin premature aging. Sunscreens labeled as "water resistant" should also specify whether they remain effective after 40 or 80 minutes of swimming or profuse sweating and they are also required to include information about the necessity of reapplication [12].

The formulation of sunscreens involves the use of different organic and inorganic substances to assure good protection, minimal side effects and good cosmetic acceptability. The most commonly used filters and its action spectra are listed on Table I.

Inorganic or physical sunscreens act reflecting or scattering the UVR, visible light, and infrared radiation. The most commonly used are zinc oxide (ZnO) and titanium dioxide (TiO2); iron oxide is added usually to better match the natural skin color [5]. New technologies such as micronization and encapsulation, which decreased the size of the particles, allowed the production of more cosmetically acceptable filters [13]. The addition of TiO2 and ZnO to nanoparticles brought further improvement, and sunscreens became more transparent, fluid and with better spreadability [14,15]. Physical sunscreens are considered biologically inert, photostable, and rarely induce allergic reactions. However, the use of nano and microparticles has raised fears about its percutaneous penetration and security. Recent studies failed to demonstrate mutagenic or cytotoxic effects in human lymphocytes after 24 h of exposure to nanoparticles of TiO2 [16,17]. In spite of that, caution is recommendable when prescribing these substances, especially to young children, until additional safety evidences become available.

The organic or chemical sunscreens act especially in the wavelengths of UVB and UVA. Most of them absorb radiation and, by photochemical reaction, decreases the energy levels, reducing the damage to cellular structures. They usually operate in restricted ranges of the UVR spectrum and are combined to ensure a broader effect. To be effective, chemical sunscreens should be stable to sunlight, able to dissolve or disperse easily remaining on the vehicle even after sweating or swimming [13].

Table I. Characteristics and actions of sunscreen agents permitted in Europe (EC) and USA (FDA)

UV filters	Permitted in	Maximum concentration (FDA/EC)	Protection range (nm)
UV filter - Inorganic			
Titanium dioxide	EC, USA	25%	290-350
Zinc oxide	EC	25%	290-400
UV filter - Organic			
Padimate O/ octyldimethyl PABA	EC, USA	8%	290-315
2-Ethylhexyl salicylate/ Octyl salicylate	EC, USA	5%	260-310
Cinoxate	USA	3%	270-328
Ethylhexyl-methoxycinnamate/ Octyl- methoxycinnamate	EC, USA	7,5[1]-10%[2]	280-310
Trolamine salicylate	USA	12%	269-320
Homosalate	EC, USA	10 [2] -15%[1]	290-315
2-cyano-3,3-diphenyl acrylic acid /Octocrylene	EC, USA	10%	287-323
2-Phenylbenzimidazole-5-sulfonic acid and its potassium,sodium and triethanolamine salts / Ensulizole	EC, USA	4[1]- 8%[2]	290-340
Benzophenone-3/Oxybenzone	EC, USA	6[1] 10% [2]	27--350
2-Hydroxy-4-methoxybenzophenone-5-sulfonic acid/ Sulisobenzone	EC, USA	10%	250-380
Dioxybenzone	USA	3%	206-380
1-(4-tert-butylphenyl)-3(4-methoxyphenyl) propane-1,3-dione /Avobenzone	EC, USA	3[1]-5%[2]	310-400
Terephthalylidene dicamphor sulfonic acid/Ecamsule/ Mexoryl SX	EC, USA	10%	295-390

[1] US Food and Drug Administration: CFR - Code of Federal Regulations Title 21. PART 352 - SUNSCREEN DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE [STAYED INDEFINITELY] Subpart B Active Ingredients. Sec. 352.10 Sunscreen active ingredients. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=352.10. Last access in 17/07/2012

[2] Council Directive of the European Committee (COUNCIL DIRECTIVE OF EC (76/768/EEC). List of the permitted UV filters which cosmetic products may contain. Annex VII, 2010; 027.001

Organic and inorganic sunscreens can also act in concert to increase the SPF, since the UV light scattering provided by physical filters increases the optical paths of the photons and its subsequent absorption by organic agents [18].

Adverse reactions to sunscreens are rare. Photoallergic reactions can occur due to the presence of benzophenone-3 (oxybenzone). The oxybenzone has a potential of systemic absorption and, in animal models, can cause endocrine changes. However, there is no evidence that it causes hormonal changes in humans, until now [19]. The PABA, amyl dimethyl PABA and the benzophenone-10 are known as photo-allergens, but are no longer used in sun protection products [13].

The benefit of using sunscreens also depends on the application of the correct amount of product and, in order to achieve the labeled SPF, an application of 2 mg/cm^2 is required [5]. Some studies show that the amount of sunscreen employed is normally around 0.5 mg/cm^2 and not spread evenly, reducing the SPF considerably [20]. For a consistent protection, sunscreens should be applied 15-30 minutes before sun exposure and reapplied every 2-3 hours, or more, in special situations such as excessive sweating and prolonged swimming [6]. The reapplication of sunscreen 15 to 30 minutes after the first pass is recommended because this strategy increases the film uniformity [21].

There are some evidences that the oral use of several substances has a preventive effect against UVR related skin damage. The mechanisms of action of such agents include antioxidant, anti-inflammatory and even immunomodulatory effects [22]. The real applicability and intensity of action of these substances still requires further investigation, but they seem to be promising co-adjuvants in relation to the holistic care and prevention of sun damage. The most cited substances that contribute to systemic photoprotection are described in Table II.

Table II. Substances with systemic photoprotection effects

Agent	Source	Effect	References
Carotenoids	Natural pigments responsible for the colors yellow, orange or red in many fruits Vegetables, egg yolks, shellfish and some fishes	Increase in the Minimal Erythema Dose (MED)	Stahl W, et al. Lycopene-rich products and dietary photoprotection. Photochem Photobiol Sci 2006; 5:238-42.
Polyphenols	Tea and Wine	Studies in animals have shown that oral intake of continuous epigallocatechin-3-gallate increase the MED and reduces UV-B. induced photocarcinogenesis and photoaging The dose of wine required for this effect has not been determined	Meeran S, et al. Inhibition of UV-B-induced skin tumor development by drinking green tea polyphenols is mediated through DNA repair and subsequent inhibition of inflammation. J Invest Dermatol 2009;129:1258-70. Moehrle M, et al. Sun protection by red wine? J Dtsch Dermatol Ges. 2009;7:29-32.
Flavonoids	Plants, fruits, vegetables	Genistin, the isoflavone found in soybeans, blocks both UV-A and UV-B radiation and reduces photocarcinogenic and photoaging effects. Quercetin is the flavonoid with the most potent antioxidant properties.	Wei H, et al. Isoflavone genistein: photoprotection and clinical implications in dermatology. J Nutr. 2003;133(Suppl 1):3811S-9S. Erden Inal M, et al.. Beneficial effects of quercetin on oxidative stress induced by ultraviolet A. Clin Exp Dermatol 2001;26:536-9.
Extract of *Polypodium leucotomos*	Fronds of *P. leucotomos* fern	Blocks the generation of reactive oxygen species and inhibits UV-induced cell death. Prevents UV-induced apoptosis and necrosis as well as degradation of the extracellular matrix, thereby reducing solar elastosis.	González S, Pathak M. Inhibition of ultraviolet-induced formation of reactive oxygen species, lipid peroxidation, erythema and skin photosensitization by Polypodium leucotomos. Photodermatol Photoimmunol Photomed 1996;12:45-56. Middelkamp-Hup M, et al. Orally administered Polypodium leucotomos extract decreases psoralen-UVAinduced phototoxicity, pigmentation, and damage of human skin. J Am Acad Dermatol 2004;50:41-9.
Caffeine	Coffee, tea, chocolate	Epidemiologic studies support the experimental evidence that caffeine consumption has a protective effect against skin cancer. Experimentally, both topical and oral caffeine promote the apoptosis of the keratinocytes irradiated with UV-B, perhaps playing a role in preventing photocarcinogenesis.	Abel E, et al. Daily coffee consumption and prevalence of nonmelanoma skin cancer in Caucasian women. Eur J Cancer Prev 2007;16:446-52. Kerzendorfer C, O'Driscoll M. UV-B and caffeine: inhibiting the DNA damage response to protect against the adverse effects of UV-B. J Invest Dermatol 2009; 129:1611-3.

It is known that much of the population has appropriate information about the deleterious effects of UVR exposure. Nevertheless, this knowledge is not translated into action and many individuals still want to get tanned and fail to practice proper sun protection behaviours [23]. Several factors influence the photoprotection conduct, including age, race, ethnicity, individual and social values, attitudes and knowledge about the personal sensitivity [24]. Adolescents and young adults are especially prone to excessive UVR exposure since, in spite of been aware of the risks, inappropriate use of sunscreen is more prevalent in this group [25-27]. In addition, a significant portion of the population use artificial tanning devices, especially among people aging 18 to 25 years and women. It was accepted, for many years, that most of the total UVR doses during lifetime were acquired before 20 years of age. Nowadays, this behavior is changing because mature adults frequently increase their outdoor activities after retirement and men do not practice proper protective measures. On the other side, teenagers are getting lower UV doses since they are staying indoors longer than before [24,25,28].

Ultraviolet radiation and neoplasias

Chronic sun exposure, especially to its UV component, is considered the main risk factor for the development of nonmelanoma skin cancer and its precursors [29]. The cumulative dose of exposure to UVR and the individual phototype are the main factors involved in photocarcinogenesis. Other aspects that influence the intensity of exposure to UVR include high altitude, proximity to the Equator and outdoor activities [29-31].

The routine use of sunscreens has proven to be effective in reducing squamous cell carcinoma and actinic keratosis, but this has not yet been proven in relation to basal cell carcinoma and melanoma [19]. A randomized controlled trial conducted in Australia, followed 1621 patients for 4.5 years. They were divided in 2 groups: one used SPF 16 sunscreen daily on sun-exposed areas and the other did not use sunscreen [32]. It was observed that there was no reduction in the incidence or total number of basal cell carcinoma, but there was a statistically significant reduction of 39% of squamous cell carcinoma among patients using sun protection. The results of a follow up of 8 years of the above study indicated that there was a 35% reduction in the incidence of new patients diagnosed with squamous cell carcinoma [33]. Furthermore, the total reduction rate for squamous cell carcinoma was 38%. In relation to basal cell carcinoma, the authors did not observe alterations in the incidence or in the total number of lesions. However, they proposed that an increase in the SPF could possibly demonstrate a trend toward decreasing the incidence of basal cell carcinoma.

With regard to melanoma, the substantiation concerning the role of photoprotection is still inconclusive [19]. A meta-analysis published in 2002 evaluated the data from 11 case-control studies (1966-1999), comparing the frequency of use sunscreen on the outcomes of melanoma. The authors concluded that there was no difference in the risk for melanoma among individuals who used sunscreen compared with those who have not used it [34]. Another meta-analysis, with 18 case-control studies, evaluated the use of sunscreen before the diagnosis of melanoma and the results failed to confirm whether they were beneficial or not [35].

Several factors must be taken into account when appraising meta-analysis results, such as lack of control studies for possible confounding factors, amount of sunscreen applied, SPF and intensity of UVA protection [36,37]. Other aspects that should be taken into consideration is that there is indirect evidence of the benefits of sunscreen on the occurrence of melanoma, since the use of SPF 30 sunscreen causes a statistically significant reduction in the development of melanocytic nevi and an increased number of melanocytic nevi is an important risk factor for developing melanoma [38,39]. Therefore, it is reasonable to consider the importance of photoprotection, especially in high-risk populations [40].

Ultraviolet radiation and systemic disorders

Several disorders can be triggered or influenced by sun exposure, particularly owing to the direct action of ultraviolet radiation on cellular processes and cytokines release [41,42].

Photosensitivity is a frequent drug-related harmful effect. Susceptible patients could present manifestations of photoallergy or phototoxicity, most commonly determined by normal ambient exposure levels of UVA radiation and, sometimes, visible light. Subtypes of drug-induced photosensitivity include pseudoporphyria, photo onycholysis, lichenoid and telangiectatic reactions and dyschromia [43].

Antibiotics such as tetracyclines and quinolones, some antinflammatories, thiazide diuretics, statins, chlorpromazine, amiodarone and some immunomodulators are among the most common substances that could induce photoallergic reactions (Fig. 1) [44-48]. Depending on the reaction severity and the importance of maintaining the drug, avoiding sunlight exposure and topical sunscreens are fundamental to prevent additional skin damage [48,49].

Lupus erythematosus (LE) is an autoimmune systemic disease that presents a variety of internal and cutaneous findings. Photosensitivity is one the most common manifestations of LE, with a clear relationship between exposure to UV light, generation of autoantibodies, cytotoxic effects and the development of photosensitivity [50,51]. LE-specific lesions may be induced or exacerbated by UVR, sunburn and phototoxic drug reactions may develop easily and other photosensitive disorders have been reported to occur more frequently in LE patients (Fig. 2) [52]. The action spectrum of UV radiation on lupic patients varies individually. Phototesting with UVA, UVB and even high intensity visible light are useful to orient better prevention and treatment strategies [51,53]. The management of photosensitivity associated with LE requires education of the patient about avoidance of excessive sun exposure, and continuous photoprotection through physical measures such as protective clothing, and daily application of highly potent chemical or physical UVA- and UVB-protective filters. Sunscreens should be applied in sufficient amount, at least 30 minutes before sun exposure, in order to avoid induction and exacerbation of cutaneous lesions [53].

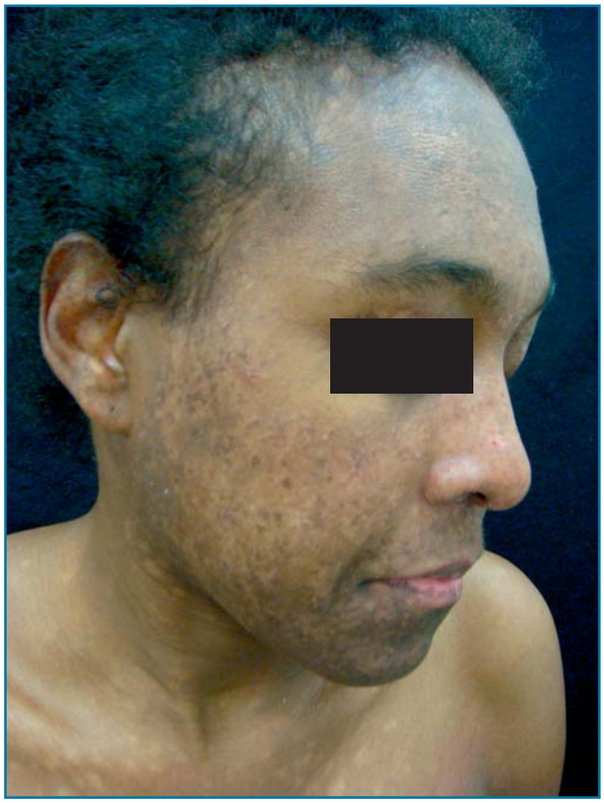

Figure 1. Photoallergic hyperchromic reaction on the face and neck of a woman under treatment with amiodarone.

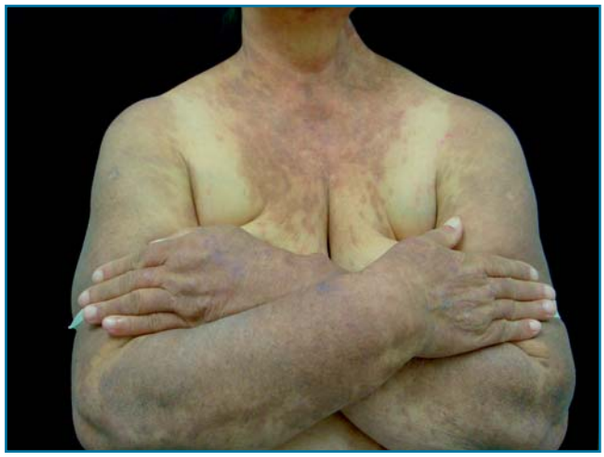

Figure 2. Photoaggravated brown-gray maculo papular lesions on the chest and extension areas of the arms of a 62 years-old women with systemic lupus erythematosus.

Ultraviolet radiation and hyperpigmentary disorders

Normal skin color varies according to ethnicity, response to environmental influences and even age. It is determined mainly by the dermal components, especially hemoglobin and melanin, epidermal melanin in keratinocytes and the morphology of the stratum corneum. Hyperpigmentation results from different physiopathological mechanisms such as : increase in the synthesis of melanin, alterations in its distribution, exogenous pigments and epidermal tickening [54].

Acquired local and generalized alterations in the intensity of pigmentation are responsible for several skin manifestations. They are an important cosmetic concern in both sexes and can cause psychological and emotional distress, with a significant negative impact on a person's health-related quality of life in many cultures [55,56]. The different causes involved in the increase of pigmentation, associated to the variability of skin responses, accounts for the complexity of its treatment and the necessity of effective preventive measures [57].

Sun exposure is one of the most important triggers of hyperpigmentation since both UVB and UVA radiation, are involved in its immediate and delayed development, in addition of increasing skin color after pigmentary incontinence secondary to inflammatory processes. In consequence, photoprotection is an important part of preventing dark marks on the skin.

Dyschromias, in particular post-inflammatory hyperpigmentation (PIH) occurring after cutaneous injury, remains a challenge in terms of management and prevention, especially in dark skinned individuals [55,56,58]. The treatment of PIH should be started early to help hasten its resolution and begins with management of the initial inflammatory condition. Caution and avoidance of aggressive procedures are fundamental to achieve good results [58]. Considering the increase in dermal melanocytes and melanin production, broad spectrum filters are the main stay of prevention. Regularity of application, independent of season and skin color, needs to be reinforced.

Melasma is a common facial hyperpigmentation affecting people worldwide. Its precise pathogenic mechanisms remain to be completely elucidated. However, epidemiological studies conducted in different geographical regions show that the pigmentation is frequently triggered or exacerbated by sun exposure [59–61]. Most of the melasma lesions start during the second or third decade of life and sun exposure was reported as a triggering factor by 51% of women and as an aggravating factor by 84% of them [60]. The risk of severe melasma could be about three times higher for women with age at onset under 30, phototype V and major lifetime sun exposure [60].

UV radiation induces melanocyte proliferation, migration, and melanogenesis and increase the production of multiple cytokines, including interleukin-1, endothelin-1, alpha-melanocyte-stimulating hormone (α-MSH), and adrenocorticotropic hormone (ACTH) from keratinocytes, which in turn upregulate melanocyte proliferation and melanogenesis [61]. Several studies have shown that light from UV to the visible spectrum can induce pigmentary changes in the skin, mainly in Fitzpatrick skin phototypes IV to VI [62]. The clear relation between induction of pigmentation and sun or light exposure make photoprotection and sun avoidance measures a critical part of melasma management, since sunscreens are effective in inhibiting the onset of melasma, preventing recurrences and in enhancing the efficacy of other topical therapies (Fig. 3) [63–65].

Effective sun protection is especially important in situations of higher risk for hyperpigmentation worsening. Pregnancy and the use of oral contraceptive or hormone replacement therapy are important co-factors for the

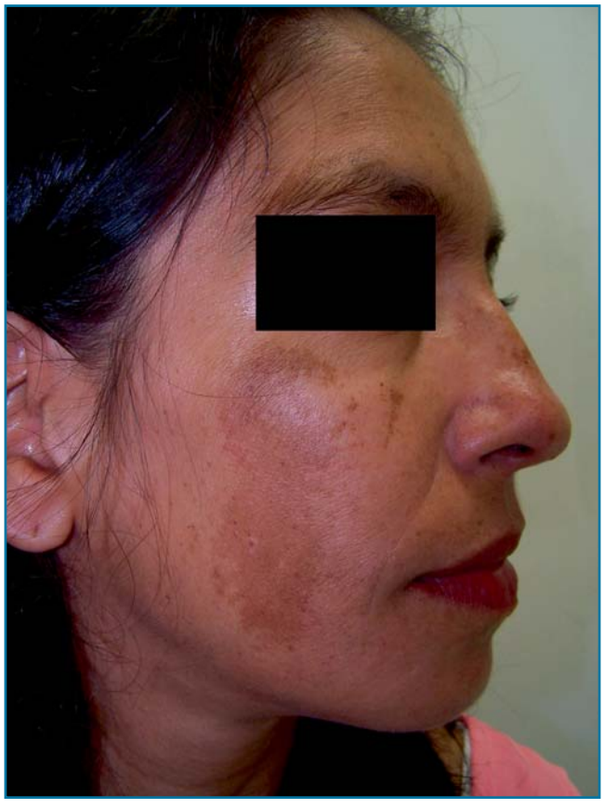

Figure 3. Melasma: hyperpigmented brownish lesion, with well-demarcated borders, on the cheek of a skin type V woman.

development or aggravation of melasma [60,66]. A double-blind placebo controlled study with 65 Latino pregnant women who received a broad spectrum sunscreen showed that melasma appearance was significantly lower in those who fully complied with the product application [67]. Another study, conducted with 200 Moroccan women, who were less than 3 months pregnant, also demonstrated that the regular use of a high UVB, UVA and visible light protection factor sunscreen diminished significantly the occurrence of melasma during pregnancy [64].

Besides depigmenting therapies, melasma patients should also be instructed to apply sunscreens daily, preferentially those with physical filters that could be used as camouflage or part of the make-up routine. Practicing sun avoidance and wearing protective hats and clothing when outdoors are also strongly recommended [65,68].

Much needs to be clarified in terms of etiopathogenesis to enhance the treatment and prevention of pigmentary disorders. A better knowledge of the rule of visible light will certainly add to better results and patient's satisfaction.

Conflicts of interest statement

T. Ferreira Cestari : none.
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Melasma and aspects of pigmentary disorders in Asians

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KEYWORDS
Melasma;
Acquired bilateral melanosis of the neck

Summary
Pigmentary changes in Asians are larger problems and more important features of aging than wrinkles. Melasma is a commonly observed epidermal hypermelanosis of the face in Asians. The altered dermal structures and impaired basement membrane are thought to have an influence on the development of epidermal hyperpigmentation of melasma. Dermal hyperpigmentary diseases are particularly common in Asians. Acquired bilateral melanosis of the neck is a characteristic dermal melanotic condition primarily of the neck in peri-menopausal women. It is characterized by marked accumulation of dermal pigment with perivascular lymphocytic infiltration. The cases seem to represent a continuum of Riehl's melanosis. Subclinical injury or inflammation may play a role as possible causative factors for the development of the pigmentation.

MOTS CLÉS
Mélasma ;
Mélanose acquise bilatérale du cou.

Résumé
Dans les populations asiatiques, les anomalies pigmentaires sont une composante du vieillissement cutané beaucoup plus importante que les rides. Parmi les hyperpigmentations faciales, le mélasma est très fréquent chez les Asiatiques. Les anomalies du derme et les altérations de la membrane basale jouent probablement un rôle dans le développement de l'hyperpigmentation épidermique du mélasma. Les pigmentations de nature dermique sont assez fréquentes chez les Asiatiques. La mélanose bilatérale du cou est une maladie particulière, de localisation dermique, qu'on observe sur la nuque chez les femmes autour de la ménopause. Elle est caractérisée par une accumulation importante de pigment mélanique dans le derme, associé à un infiltrat inflammatoire lymphocytaire périvasculaire. Cette maladie pourrait appartenir au spectre de la mélanose de Riehl. Des traumatismes mineurs ou de nature inflammatoire pourraient être en cause dans ce type de pigmentation.

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Introduction

In Asians, pigmentary changes are larger problems and more important features of aging than wrinkles. Melasma is a common epidermal hypermelanosis of the face. The dermal melanocytoses such as nevus of Ota and acquired bilateral nevus of Ota-like macule (ABNOM) occur almost exclusively in Asians. Incidence of postinflammatory hyperpigmentation (PIH) is higher in the darker skin. This review addresses the current understanding of pathogenesis of melasma, the most intractable pigmentary disorder, and introduces the characteristics of a unique dermal melanotic disorder, acquired bilateral melanosis of the neck in peri-menopausal Korean women (Fig. 1).

Current understanding of melasma pathogenesis

Pigmentary changes

Melasma was formerly classified histopathologically as epidermal, dermal, or mixed type according to the pigment depth [1]. However, current histopathological studies of melasma consistently report that the increased epidermal pigmentation is the hallmark of melasma and must be the main target for melasma treatment [2–4]. The lesional skin is characterized by increased melanin deposition throughout the epidermis. There was an 83% increase in epidermal pigmentation in lesional skin of 56 Korean melasma patients compared to perilesional normal skin [2]. Recent transcriptomics study of Korean melasma had showed upregulation of many melanin biosynthesis-related genes such as Tyrosinase, TYRP1, TYRP2 and MITF in the lesional skin [5]. Immunohistochemical staining had also showed that the protein expression levels of these genes were higher in the lesional skin. Therefore, it is clear that increased melanogenesis in melanocytes induces epidermal hyperpigmentation which results in hyperpigmented patches on the face.

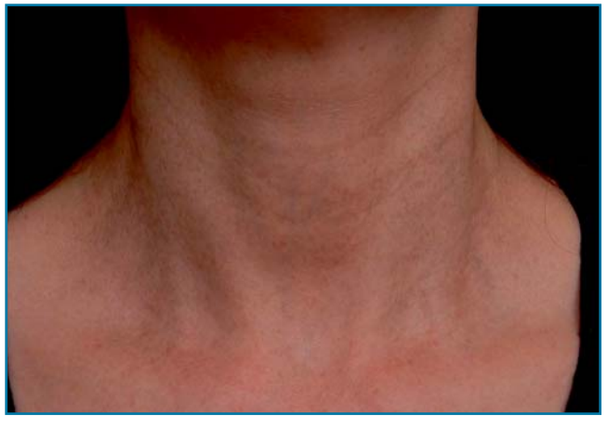

Figure 1. Acquired bilateral melanosis of the neck in perimenopausal women. The pigmentation exclusively involved the neck, and is characterized by bilateral, symmetrical brown-to-gray patchy or mottled pigmentation.

Some patients (36% in Korean, 45% in Indian) have dermal melanin in addition to the epidermal melanin in the lesional skin [2,4]. However, the significance of dermal melanin in melasma is doubtful. The amount of dermal melanin is not significant compared to that of perilesional normal skin [2,3]. Moreover, the distribution is heterogeneous in the melasma lesional skin [6]. It was noticed that in Caucasian melasma, dermal melanin levels were too low to be detected [5]. The dermal melanin in melasma seems to be commonly found in melasma patients with Fitzpatrick skin types III to V [2–4]. All melasma patients with skin type IV to V have dermal melanin as well as increased epidermal melanin in lesional skin of melasma [4]. Dermal melanins are even found in the normal facial skin of Korean and Japanese [2]. Therefore, further study is needed to determine if this small amount of dermal melanin in the melasma lesional skin does really affect the therapeutic outcome of the treatment.

Basement membrane perspective

Recent histological studies of melasma have described changes in the basement membrane in melasma lesional skin [7,8]. The basement membrane structure in lesional skin is not intact and looks disrupted. The overall type IV collagen expression was significantly reduced in lesional skin compared with perilesional normal skin [7]. The feature was more evident at the margin of some melanocytes, showing a feature of protruding into the dermis, so called pendulous melanocytes. The MMP2 protein and mRNA expressions were markedly increased in the lesional skin compared to the perilesional normal skin. It was suggested that chronic UV irradiation may be responsible for the loosening of basement membrane through up-regulation of MMP2 expression in melasma because MMP2 immunoreactivity was co-localized with elastotic materials.

What role does the impaired basement membrane have in melasma pathogenesis? It may be that the loosening of basement membrane facilitates the pendulous change of the melanocytes. The pendulous cells may easily drop into dermis or become destroyed when traumatic events including laser treatment are given. The destroyed melanocytes would leave heavy pigmentation in the dermis resulting in hyperpigmentation during treatment.

The other speculation which may be more meaningful is that the changes may facilitate the interaction between dermal structures and epidermal melanocytes. Indeed, the lesional skins of melasma have alterations in dermal structures in addition to pigmentation changes, suggesting a role of dermis for melasma development [9–11]. The network of cellular interactions between fibroblasts and perhaps vasculatures and melanocytes during chronic sun exposure may play an important role in development of melasma [12]. They may work in conjunction to stimulate melanocytes resulting in epidermal hyperpigmentation.

Vascular perspective

Melasma dermal skin is different from perilesional normal skin and shows features of prominent solar damaged skin. Increased solar elastosis in lesional skin was a predominant finding, suggesting UV exposure in the pathogenesis [9]. It

was also shown that melasma is characterized by increased vasculature in the lesional skin both clinically and histologically [11]. Melasma patients have additional features like telangiectatic erythema confined to hyperpigmented skin. The erythema index was significantly higher in the lesional skin than in the perilesional normal skin. Immunohistochemistry for vascular markers revealed increased numbers of vessels in the upper dermis. The number of vessels had a positive relationship with epidermal pigmentation in melasma lesional skin.

Although the role of cutaneous blood vessels in the pathogenesis of melasma remains unclear, recent study suggested that targeting blood vessels along with the melanin pigment is beneficial for the treatment of melasma [13]. A prospective, controlled, comparative split-face study evaluating the effects of pulsed dye laser (PDL) therapy in association with triple combination cream in the treatment of melasma was performed. The combination of the Triluma cream and PDL induced a significant decrease in the pigmentation as compared to cream alone. Interestingly, the improvement induced by the combination of PDL and the cream remains significant even after one summer while relapses were observed in the group treated with only the cream. This suggested that targeting vascularization in the melasma lesions may decrease the stimulation of melanocytes. The other study has shown that the treatment of melasma with tranexamic acid decreased epidermal pigmentation associated with melasma and also reversed melasma-related dermal changes such as vessel number [14]. Future studies are needed to investigate the possible connection between blood vessels and cutaneous pigmentation.

Acquired bilateral melanosis of the neck in peri-menopausal women

Pigmentary disorders that are particularly common in Asians include dermal hyperpigmentation (melanocytotic or melanotic). Nevus of Ota and ABNOM are well-known dermal melanocytoses characterized clinically by blue-grey pigmentation. These pigmentation disorders are most responsive to Q-switched laser therapy and are treatable disorders, while idiopathic dermal melanosis remains a challenging condition to treat, and the etiology is still unclear.

Acquired bilateral melanosis of the neck in peri-menopausal women has been recently recognized [15]. The pigmentation exclusively involves the neck and is characterized by bilateral, symmetrical brown-to-gray patchy or mottled pigmentation on the lateral neck (Fig. 1). The dominant histologic feature is marked accumulation of dermal pigment with perivascular lymphocytic infiltration, consistent with PIH. However, predisposing factors were not found. Subclinical injury or inflammation is a possible cause of the development of pigmentation. None of treatments including laser or intense pulsed light brought good responses. It is common to see higher risk of PIH and even aggravation of the pigmentation following treatment.

Riehl's melanosis, also known as pigmented contact dermatitis, presents with diffuse, reticular patches of brown-gray hyperpigmentation that develops rapidly over the face and neck [16]. It is common in middle aged women with darker skin types. The dominant histologic feature is liquefaction degeneration of epidermal basal layer, resulting in pigment incontinence into the dermis. The etiology is largely unknown, but it is believed to be primarily due to contact sensitivity to chemical agents. However, more cases have been described with no identified causative agents. Considering that the diagnostic criteria of Riehl's melanosis are not clearly established so far, the acquired bilateral melanosis of the neck observed in peri-menopausal women seems to represent a continuum of Riehl's melanosis.

Conclusion

Melasma is characterized by epidermal hyperpigmentation. The altered dermal structures and impaired basement membrane may have an influence on the development of epidermal hyperpigmentation of melasma. All of these features should be considered for melasma treatment. The role of vascularization in the pigmentation processes definitely needs to be studied further.

Acquired bilateral melanosis of the neck is a dermal melanotic condition primarily of the neck in peri-menopausal women. The pathogenesis is largely unknown and the treatment is still challenging.

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Conflicts of interest statement

H.Y. Kang: none.

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Mechanisms underlying post-inflammatory hyperpigmentation: lessons from solar lentigo

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KEYWORDS
Post-inflammatory hyperpigmentation;
Melanogenesis;
Dermal/epidermal cross-talk;
Solar lentigo

Summary
Hyperpigmentation of the skin is a common dermatologic condition in all skin types but most prominent in brown-skinned population. In skin of color any inflammation or injury can be accompanied by alterations in pigmentation (hyper/hypo-pigmentation). Post-inflammatory hyperpigmentation (PIH) can be observed in many skin conditions including acne, eczema, and contact dermatitis. In the control of skin pigmentation, parallel to the cross-talk between keratinocytes and melanocytes, increasing evidence has underlined the crucial role exerted by the interactions between mesenchymal and epithelial cells through the release of fibroblast-derived growth factors. Among these factors, the keratinocyte growth factor (KGF), alone or in combination with interleukin-1α, induces melanin deposition *in vitro* and hyperpigmented lesions *in vivo*. Furthermore, a moderate increase of KGF and a high induction of its receptor have been shown in solar lentigo lesions, suggesting the involvement of this growth factor in the onset of the hyperpigmented spots. Several studies highlight the possible contribution of the fibroblast-derived melanogenic growth factors to the hyperpigmentated lesions, in the context of the mesenchymal – epithelial interactions modulating melanocyte functions.

MOTS CLÉS
Hyperpigmentation post-inflammatoire ;
Mélanogenèse ;
Interaction derme épiderme et lentigo actinique

Résumé
Les hyperpigmentations cutanées sont une des dermatoses les plus fréquentes sur tout type de peau, mais ceci est particulièrement vrai dans les populations à peau foncée. Dans les phototypes foncés, toute inflammation ou traumatisme peut se traduire par des altérations de la pigmentation, qu'il s'agisse d'hyperpigmentations ou d'hypopigmentation. Les pigmentations post-inflammatoires peuvent être observées dans de nombreuses maladies cutanées, notamment l'acné, la dermatite atopique et l'eczéma de contact. On sait que le contrôle de la pigmentation résulte d'interactions entre les kératinocytes et les mélanocytes, mais il y a de plus en plus de données soulignant le rôle crucial des interactions entre les cellules mésenchymateuses et épithéliales, grâce à la production de

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facteurs de croissance par les fibroblastes. Parmi ces molécules, le facteur de croissance kératinocytaire (KGF), seul ou en association avec l'interleukine 1-α, peut provoquer des dépôts de mélanine *in vitro* et des lésions hyperpigmentées *in vivo*. De plus, on a montré que dans les lésions de lentigo actinique, il existe une augmentation modérée du facteur de croissance kératinocytaire et une importante induction de son récepteur ; ceci suggère un rôle de ce facteur de croissance dans l'apparition des taches hyperpigmentées. Plusieurs études ont souligné aussi l'importance des facteurs de croissance mélanocytaires produits par les fibroblastes dans la genèse des lésions hyperpigmentées, soulignant ainsi l'importance des interactions mésenchyme-épithélium dans le contrôle de la fonction mélanocytaire.

Introduction

Post-inflammatory hyperpigmentation (PIH) of the skin is a pigmentary disorder that is seen in all skin types, but remains a hallmark of skin of color [1]. In darker skinned individuals, any inflammation or injury to skin can be accompanied by alterations in pigmentation, either hyperpigmentation or hypopigmentation. PIH can be caused by endogenous inflammatory skin disorders or iatrogenic sources (lasers). It can be observed in many skin conditions including acne, eczema, and contact dermatitis and can be diffuse or localized, depending on the distribution of the preceding inflammation. PIH is characterized by increased melanocytic activities and dermal melanophages. This condition tends to be worse in patients whose preceding inflammatory disease, such as lichen planus and lupus erythematosus, has disrupted the basal layer of the epidermis [2]. A variety of topical agents are available to reduce the hyperpigmentation [3].

Cutaneous paracrine network in skin pigmentation

Human skin color is mainly due to melanin pigments produced by melanocytes and transferred to neighboring keratinocytes via their dendrites. Constitutive pigmentation depends on the quantity and the quality (pheo/eumelanin ratio) of the melanin produced, as well as the size, mode of transfer, distribution and degradation of the melanosomes inside the keratinocytes and not on the number of melanocytes which is relatively constant. Keratinocytes are also crucial in regulating the adhesion, proliferation, survival, and morphology of melanocytes. The cross-talk between melanocytes and keratinocytes is mediated by a paracrine effect through keratinocyte-derived soluble factors including α-melanocyte-stimulating hormone (α-MSH), endothelin 1 (ET-1), stem cell factor (SCF), basic fibroblast growth factor (bFGF), prostaglandin E2 and F2 alpha (PGE2, PGF2α), hepatocyte growth factor (HGF) [4,5]. Keratinocytes also modulate the transcription of melanogenic proteins and subsequently the quantity and quality of melanin [6]. Furthermore, keratinocytes, via the increase in numerous released cytokines, are strongly involved in the pro-pigmenting response of melanocyte after UV exposure [5,7-9]. Even though the role of the dermal compartment on pigmentation is far less documented, there is now evidence, that the mesenchymal compartment including fibroblasts and fibroblast-derived extracellular matrix (ECM) proteins, influences melanocyte proliferation, apoptosis resistance, morphology and melanogenic activity [10-15]. Dermal fibroblasts play a regulatory role in constitutive pigmentation through the secretion of soluble factors [14]. Some are specifically secreted by fibroblasts such as Dickkopf-1 (DKK1) which is responsible for the very light color of the palms and soles via a suppressive effect on melanocyte activity and melanin uptake by keratinocytes [13,15]. More recently, the pro-pigmenting effect of Neuregulin-1 secreted by fibroblasts derived from dark skin suggests its involvement in determining human skin color [11]. Furthermore, paracrine cytokines regulation loop also exist: keratinocyte-produced cytokines, such as interleukin-1 alpha (IL1-α) or TNF-α, stimulate fibroblasts which in turn release melanocyte stimulating factors such as SCF and HGF [16]. Deregulations of melanocyte homeostasis and/or melanogenesis are the cause of various hyper/hypopigmented lesions. For a better understanding of the pigmentation mechanisms and their deregulations, *in vitro* systems have been developed that reproduce the physiology of the pigmentary system. These models reproduce key structures of native skin especially a three-dimensional organization and a differentiated epidermis [17,18]. To overcome the absence of fibroblasts in these reconstructed epidermis, more complex organotypic pigmented skin models reconstructed on a dermal equivalent containing fibroblasts, have been designed [10,12,19-22]. In order to study human skin pigmentation in a highly physiological *in vitro* model, Duval et al. [23] have reconstructed a pigmented skin model, including human normal melanocytes, keratinocytes and fibroblasts able to develop a real constitutive pigmentation (melanin production and transfer) and able to respond to known stimulators. They demonstrated that the normalization of keratinocyte differentiation using KGF, a paracrine growth factor produced by mesenchymal cells allowed an active pigmentation, as shown by the expression of key melanogenic markers, the production and transfer of melanosomes into keratinocytes. Furthermore, induction of pigmentation was achieved by treatment with known pro-pigmenting molecules, α-MSH and forskolin, thus demonstrating the functionality of the pigmentary system. This pigmented skin model represents a useful tool to study the mesenchymal-epithelial interactions in the control of skin pigmentation.

Post-inflammatory hyperpigmentation

PIH represents the sequelae of inflammatory disease processes such as infections, allergic reactions, phototoxic eruptions and trauma [24]. PIH frequently appears after the regression of different inflammatory cutaneous disorders including lichen planus, lupus erythematosus, bullous pemphigoid, herpes zoster and more common skin diseases such as atopic dermatitis and acne vulgaris [2,25]. It is thought that PIH occurs through the oxidation of arachidonic acid by peroxidase, cyclooxygenase and 5-lipoxygenase to intermediates that form prostaglandins, leukotrienes and thromboxanes. These stimulate epidermal melanocytes to become hypertrophic, leading to increased synthesis of melanin and the transfer of pigment to surrounding keratinocytes and dermal macrophages. The result is the appearance of hyperpigmented lesions with indistinct, feathered borders that vary in size, shape and colour [26,27].

PIH is commonly induced by acne lesions, most prevalently in the darker Fitzpatrick skin types IV- VI [28-31]. Therefore, a major issue in treating acne in skin of colour is the need to treat and prevent PIH. Topical retinoids are considered a key component of the treatment regimen for acne vulgaris because they play a role in blocking the development of both acne and PIH [28,32-34].

Solar lentigo as a model of hyperpigmentary disorder

Melanocytes play an important role in the protection of skin from ultraviolet (UV)-induced damage by producing melanin whose synthesis is catalysed by melanogenic enzymes. Acute or persistent UV exposure evokes an inflammatory reaction including formation of topical oedema and erythema, which results in hyperpigmentation of skin as evidenced by formation of melasma, age spots, liver spots, freckles and lentigines. Therefore factors that mediate inflammation after UVB irradiation, such as bFGF, histamine, ET-1 and PGE2, are thought to be targets for developing skin-lightening agents after UV exposure. Solar lentigo (SL) is characterized by hyperpigmented lesions occurring in photodamaged skin areas which increase in number and size upon chronological ageing [35]. The histology of SL lesions reveals a hyperpigmented basal layer with an unchanged or slightly increased melanocyte number and an elongation of rete ridges above solar elastosis. Compared with perilesional skin, the basement membrane of SL lesions is disorganized, and their dermis contains more melanophages [36-39]. The molecular mechanisms involved in the initiation and formation of SL spots are not completely understood. Pigmentary proteins like tyrosinase (TYR), TYR-related protein-1, proopiomelanocortin, ET-1, endothelin receptor B and SCF and its receptor (c-KIT) are all increased in SL lesions [36,40-42]. Interestingly, two recent gene-profiling studies listed several inflammatory molecules that are up-regulated in SL [36,43]. The KGF binds to the KGF receptor (KGFR) which is expressed predominantly on epithelial cells, and mediates mesenchymal- epithelial interactions. It plays a role in wound healing [44] and in the regulation of hair follicle development. In addition, KGF acts on keratinocytes to induce melanosome phagocytosis [45]. This effect is more pronounced in light skin-derived keratinocytes, which express more KGFR than dark skin-derived keratinocytes [46]. Keratinocytes exposed to ultraviolet B (UVB) produce the inflammatory mediator IL-1α which in turn stimulates fibroblasts to produce KGF. Chen et al. [47] analysed the mechanisms involved in the initiation or in the maintenance of SL. They reported that KGF, alone or in combination with IL-1α, increases melanin deposition *in vitro* and induces hyperpigmentary lesions with elongated rete ridges *in vivo* with histological resemblance to human SL. Lin et al. [48] investigated the association of KGF/KGFR and pigmentary genes with the progression of SL development. An increase in TYR-positive cells and expression was found throughout SL progression, as compared to normal skin. The levels of KGF, KGFR, SCF, Ki67 (marker of proliferation) and protease-activated receptor-2 (PAR-2) varied during SL progression. Ki67, Keratin 15 (K15) and KGF/KGFR were significantly up-regulated at early-mid SL stages. The latest-stage SL expressed the lowest levels of KGF, KGFR, SCF, Ki67 and PAR-2. The increase in KGF levels might promote excessive melanosome transfer, resulting in melanin overloads within SL keratinocytes. The reduced KGF/KGFR levels in mature SL might affect both the proliferative and the phagocytic ability of the SL keratinocyte, further interfering with the melanosome transfer. The findings on the expression patterns of KGF/KGFR and other genes during SL macules development reflect on the molecular and cellular mechanisms involved in SL formation and maintenance. Intervention of these pathways, and in particular of the KGF pathway, might prevent the formation of new SL macules, slow SL progression and possible reverse the development of newly forming SL lesions. Studies focused on the alteration in the cytokine paracrine network known to regulate pigmentation, demonstrating the up-regulation of the ET-1 /ETB receptor cascade and of SCF in the SL lesional epidermis [41,42]. The tumour suppressor protein, p53, which promotes UV-induced pigmentation by transcriptional activation of proopiomelanocortin [49], has been shown to be involved in the formation of hyperpigmented spots through the regulation of melanogenic cytokine networks both in keratinocytes and in melanocytes [50]. Parallel to the cross-talk between keratinocytes and melanocytes, increasing evidence underlines the crucial role exerted by the interactions between mesenchymal and epithelial cells in the control of skin pigmentation through the release of fibroblast-derived growth factors. Cardinali et al. [45,46] have demonstrated that KGF stimulates melanosome transfer promoting the phagocytic process directly through KGFR activity and signalling on keratinocytes. Overexpression of SCF and HGF by fibroblasts has been demonstrated in hyperpigmentary disorders such as dermatofibroma and café-au-lait macules [51,52]. A positive staining for SCF, HGF and KGF has been demonstrated in fibroblasts of two cases of generalized, progressive dyschromatosis disorder [53]. Kovacs et al. [54] analysed the possible contribution of the fibroblast-derived melanogenic growth factors to the hyperpigmentation of SL, in the context of the mesenchymal- epithelial interactions modulating melanocyte functions. In particular they analysed the involvement of the HGF, KGF and SCF in SL hyperpigmentation evaluating whether the photoageing process occurring in fibroblasts could be responsible for the altered expression of these cytokines. Moreover they investigated a new possible role of KGF in regulating pigmentation through the specific induction of melanogenic cytokines by keratinocytes. Results

showed positive staining for HGF, KGF and SCF in the upper dermis of SL lesions and a significant induction of the three cytokines in photoaged fibroblasts. In addition KGF was able to specifically modulate the expression of SCF in keratinocytes. In conclusion, they suggest that fibroblasts may be persistently activated by UV exposure to release melanogenic growth factors and this inducible cytokine network acts both directly and indirectly through keratinocytes and may contribute to the hyperpigmentation of SL.

Conclusions

Several experimental and clinical data demonstrated that a considerable intercellular complexity exists between melanocytes and the other cell types proximal to them. Skin pigmentation is regulated by a complex melanogenic network in which both keratinocytes and fibroblasts synthesize growth factors and cytokines able to modulate melanocyte activities. Inflammatory conditions influence cutaneous pigmentation through the cytokine-induced activation of downstream signals able to stimulate melanogenic activity. Consequently this complex network has to be taken in consideration to develop new therapeutic strategies to treat hyperpigmentary disorders.

Conflicts of interest statement

G. Cardinali: none.
D. Kovacs: none.
M. Picardo: none.

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Topical treatment of hyperpigmentation disorders

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KEYWORDS
Hyperpigmentation,
Hydroquinone,
Skin lightening,
Depigmenting agents,
Tyrosinase inhibitors

Summary
Hyperpigmentation has traditionally been a relatively difficult condition to treat, especially in darker racial ethnic groups. Multiple topical agents available act upon different steps of the pigmentation pathway. We review these topical agents, their mechanisms of action, and their effectiveness as monotherapy and in combination with other compounds. Ultimately, combination therapy is the most efficacious when considering overall depigmentation as well as treatment time required to achieve clinical improvement.

MOTS CLÉS
Hyperpigmentation,
Hydroquinone,
Éclaircissement cutané,
Dépigmentants locaux,
Inhibiteur de la tyrosinase

Résumé
Les maladies pigmentaires sont classiquement considérées comme très difficiles à traiter, notamment sur peau foncée. Les nombreux agents topiques disponibles agissent sur différentes étapes de la pigmentation. Nous présentons une revue de ces substances à usage local, en précisant leur mécanisme d'action et leur efficacité en monothérapie ou en association avec d'autres molécules. In fine, les traitements combinés sont les plus efficaces en termes de diminution de la pigmentation et de durée de traitement nécessaire pour obtenir une amélioration clinique significative.

Introduction

There are numerous causes of hyperpigmentation, among them post-inflammatory etiologies, hormonally mediated factors, cosmetics, drug-induced causes, and ultraviolet radiation, in addition to systemic conditions such as Addison's disease, Wilson's disease, and hemochromatosis.

Historically, hyperpigmentation has been an extremely difficult entity to treat, regardless of etiology. Although numerous

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topical agents have been proven effective (Table 1), the level of clinical success with each varies, as does duration of treatment. It is imperative to individualize the choice of agent according to each patient's specific situation and expectations. In this paper, we will discuss the unique characteristics and mechanisms of action of each depigmenting agent.

It is important to note, however, that there are few published studies of the newer compounds. Additionally, most published studies of these newer agents have been conducted on small sample sizes.

Tyrosinase inhibitors

Hydroquinone

Hydroquinone has been available for medical use since the 1960s. It is available by prescription in strengths up to 4%, with higher concentrations available as a compounded product. Even with diligent application, hydroquinone takes 3 months or more to produce clinical results, and contact dermatitis is often reported. In a randomized, prospective, double-blind clinical trial performed by Haddad et al comparing 4% hydroquinone to placebo, improvement in hyperpigmentation was seen in 76.9% of patients on hydroquinone. However, 25% of those treated with hydroquinone reported adverse effects, most commonly an "itchy eruption" [1]. Combining hydroquinone with another product, such as glycolic acid, vitamin C, or vitamin E, may improve efficacy and shorten the time necessary to achieve visible results [2].

It is a relatively common practice to compound hydroquinone with a topical retinoid and corticosteroid. This triple combination was originally described in 1975 by Kligman and Willis. By combining 5% hydroquinone with 0.1% tretinoin and 0.1% dexamethasone, they achieved complete depigmentation. However, the results could not be duplicated when any component of the compound was removed [3]. Chan et al compared 4% hydroquinone to a combination of 0.01% fluocinolone acetonide, 4% hydroquinone, and 0.05% tretinoin, and found that while the combination was more effective than hydroquinone monotherapy in skin lightening, it also increased irritation [4]. Several other studies analyzing the effects of double and triple combination therapy have demonstrated similar clinical results [5,6]. This grouping of agents acts upon many mechanisms of pigmentation production, thus providing a better approach to treatment than monotherapy products alone.

Arbutin

Arbutin is a naturally occurring derivative of hydroquinone that also exerts its antimelanogenic activity via tyrosinase inhibition [7,8]. Akiu et al further confirmed this mechanism of action and reported a decrease in the melanin content of cells treated with arbutin by as much as 39% [9]. A comparative study was performed by Lei et al, who examined cocultures of melanocytes and keratinocytes treated with various depigmenting agents, including arbutin and hydroquinone. Arbutin was found to be less toxic than hydroquinone at the molecular level, resulting is less dendrite loss or aberrant morphology. This may explain its comparatively gentler effect clinically. Additionally, the effects of arbutin on tyrosinase activity and melanin content were dose-dependent [10]. However, the necessary quantity to be applied and concentration required to attain the same effects as hydroquinone have not been defined.

Aloesin

Aloesin, a compound derived from aloe, has potent antioxidant and anti-inflammatory properties [11]. It also affects melanogenesis by reducing tyrosinase activity and with it, melanin content.

The depigmenting effects of aloesin tend to be dose-dependent [12]. Its action can be potentated by the addition of arbutin. In one study, a mixture of aloesin and arbutin on cultured melanocytes produced a significant decrease in melanin content [13].

Table 1
Classification of topical depigmenting agents by mechanism of action.

Tyrosinase inhibition	Melanosome transfer inhibition	Cell turnover induction	ROS Scavengers
Hydroquinone	Soy-Derived Products	Retinoids	Ascorbic acid
Arbutin	Niacinamide	Glycolic acid	Alpha-lipoic acid
Aloesin	Retinoids	Salicylic acid	Lignin peroxidase
Azelaic acid			
Kojic acid			
Licorice extract			
Proprietary oligopeptide			
Phenylethyl resorcinol			
Mequinol			

Azelaic acid

Azelaic acid is a dicarboxylic acid that inhibits melanogenesis by preventing tyrosinase activity [14], and by interfering with DNA synthesis in overactive melanocytes [15]. Azelaic acid can be combined with taurine for synergistic antimelanogenesis effects without significant cytotoxicity [16].

Kojic acid

Kojic acid has been shown to exert its depigmenting effects through various mechanisms. Cabanes et al suggested that kojic acid inhibits catecholase activity of tyrosinase [17]. Choi *et al*. studied the production of interleukin-6 (IL-6) by kojic acid in keratinocytes, and attributed its antimelanogenic effects to this protein [18]. Kojic acid can be combined with hydroquinone, glycolic acid, or antioxidants to enhance its effectiveness.

Licorice extract

The usefulness of licorice extract in the treatment of hyperpigmentation is due to the action of its main ingredient, glabridin. Glabridin not only inhibits tyrosinase activity and UVB-induced pigmentation, but it also exerts anti-inflammatory properties by inhibiting free radical formation [19]. Liquiritin cream, a licorice extract-containing compound, has been reported to disperse melanin and improve the appearance of melasma significantly without considerable adverse effects [20].

Proprietary oligopeptide products

A relatively new skincare system contains 0.01% oligopeptide cream, an antioxidant cleanser, 20% glycolic acid lotion, and physical sunscreen.

In studies of melasma patients treated with this combination of ingredients, significant improvement in pigmentation was seen in all patients, with one patient in a 2012 study achieving complete clearance [21,22].

Phenylethyl resorcinol

Another new combination of active ingredients has been introduced to the market, containing the following ingredients: phenylethyl resorcinol, which inhibits tyrosinase activity; leucine, a competitive inhibitor/precursor of melanin formation; and undecylenoyl phenylalanine, which minimizes sun-induced melanin formation. Gold et al found this combination decreased the appearance of facial lentigines by up to 43% when used twice daily for 12 weeks in conjunction with regular application of sunscreen [23].

Mequinol

Mequinol's mechanism of action is largely unknown [24], but it is thought to act as a competitive inhibitor of tyrosinase substrates. It can be used as monotherapy, but shows increased efficacy when combined with tretinoin [25].

Free radical scavengers

Free radical scavengers, such as ascorbic acid and alpha-lipoic acid, have depigmenting properties, as well. Vitamin C interacts with copper ions at the site of tyrosinase activity to decrease pigmentation. Ascorbic acid's antimelanogenic effects on UVA- and nitric oxide-mediated melanin stimulation have been demonstrated in several studies [26]. Additionally, vitamin C deficiency has been linked to increased UVB-induced cutaneous pigmentation [27].

Alpha-lipoic acid plays a role in pigmentation as well as in the treatment of diabetes, HIV, and ischemia-reperfusion injury [28]. Its role as a depigmenting agent is a result of its antioxidizing effects. Even at low concentrations, alpha-lipoic acid has been shown to improve ultraviolet radiation-induced photodamage through inhibition of nuclear factor kappa B (NF-κB) [29].

It is important to note that concurrent use of products such as retinoids may increase the depigmentation effect of vitamin C and α-lipoic acid by assisting in penetration.

Melanosome transfer inhibitors

Soy-based products

The effectiveness of soy-based products in the treatment of hyperpigmentation is a result of their activity as serine protease inhibitors to prevent phagocytosis of melanosomes by keratinocytes [30]. Keratinocytes express protease-activated receptor 2 (PAR-2), which regulates melanosome transfer from melanocytes [31]. Utilizing products that affect this receptor pathway impact pigmentation.

Paine et al studied certain soy-derived serine proteases, soybean trypsin inhibitor (STI) and Bowman-Birk inhibitor (BBI), and their effect on pigment alteration in culture. They also examined the effects on keratinocyte phagocytosis of melanosomes and receptor peptide cleavage. These soybean-derived serine protease inhibitors were found to significantly reduce pigment, including UVB-induced pigmentation *in vivo*, by inhibiting melanosome transfer and trypsin-induced PAR-2 cleavage [32].

A relatively new product known to be useful in the treatment of hyperpigmentation is lignin peroxidase. It is derived from the tree fungus *Phanerochaete chrysosporium* and has been shown to be less irritating than alternative treatment options, such as hydroquinone.

In a randomized, double-blinded, placebo-controlled, split-face study, Mauricio et al discovered that lignin peroxidase was significantly more effective than both placebo and hydroquinone in treating hyperpigmentation. Moreover, a significant lightening effect was achieved within 8 days of initiating therapy [33]. Lignin breaks down existing melanin, but does not prevent pigment formation, so the addition of a product such as hydroquinone is advised to prevent ongoing pigmentation.

Niacinamide

Niacinamide is used as an adjunct to other therapeutic agents for multiple dermatological conditions, including acne, rosacea, and psoriasis. In patients with hyperpigmentation, it causes skin lightening by reducing melanosome transfer [34]. In a double-blind, randomized study comparing topical niacinamide 4% with hydroquinone 4% in the treatment of melasma, the lightening effect accomplished with niacinamide was not significantly different from that of hydroquinone, and results were seen slightly earlier with hydroquinone. However, niacinamide was less irritating [35]. N-nicotinoyl dopamine, a derivative of niacinamide, has been shown to have intense antioxidant properties and has successfully induced skin depigmentation without damaging the viability of the cells. Treated melanocyte morphology and overall histology remained intact and, clinically, no skin irritation was observed [36].

Cell-turnover inducers

Retinoids are a common treatment for hyperpigmentation and can be used as monotherapy as well as in combination with other topical medications. Retinoids have a dual mechanism of action in treating hyperpigmented lesions: in addition to inhibiting melanosome transfer, they also stimulate cell turnover, thus discarding melanized keratinocytes [37].

In one study, topical tretinoin 0.1% had improved facial hyperpigmentation in 90% of patients at the end of the 40-week study period [38]. In another study of patients with darker skin, tretinoin 0.1% in darker skin, not only improved hyperpigmentation, but also caused the patients'natural skin color to lighten somewhat [39]. Therefore, care must be taken when prescribing retinoids for darker Fitzpatrick skin types. Also, given the lengthy amount of time required for retinoids to produce clinically apparent results, they are usually used in combination with other topical agents and for maintenance therapy.

Glycolic acid

Chemical peels have also been used successfully in skin lightening, both as treatment and as preparation for other topical products. Glycolic acid is an alpha-hydroxy acid derived from sugarcane, and its effect is dependent upon the concentration that is used. In low concentrations, it produces rapid desquamation of keratinocytes. In higher concentrations, it produces epidermolysis. Superficial glycolic acid peels can be useful in melasma and even in post-inflammatory hyperpigmentation [40]. In a randomized, double-blinded, split-face clinical trial in which a series of tretinoin 1% peels was compared with glycolic acid 70% peels, similar depigmentation results were achieved with both processes. However, patients experienced less discomfort with tretinoin [41].

Superficial salicylic acid peels performed with concentrations ranging from 20%-30%, have revealed mixed results in the treatment of hyperpigmentation [42,43]. One study of melasma found equally effective pigmentation reduction with Jessner's solution as compared to 30% salicylic acid [44]. Salicylic acid is gentler than glycolic acid and, therefore, is useful in darker skin types. It is also useful as an introductory peel in patients with reservations about this treatment modality.

Although this review has focused on topical agents for the treatment of hyperpigmentation of various etiologies, it is necessary to mention that laser technology can be a safe and effective treatment option. Laser therapy is controversial in melasma treatment, but has shown great success with solar lentigines. The Q-switched ruby and Q-switched Nd:YAG lasers have been widely used with great success. The low-fluence Q-switched Nd:YAG has been shown to be superior to both high-fluence laser therapy of the same wavelength and glycolic acid peels for the resolution of hyperpigmentation [45].

Conclusion

In our clinical experience, hyperpigmentation is one of the most common conditions for which patients seek dermatological treatment, particularly in darker racial ethnic groups. Complete resolution can be difficult to achieve in certain conditions, such as melasma. We have reviewed several topical treatment options and their various mechanisms of action. To this day, hydroquinone and hydroquinone-containing combination compounds continue to be the mainstay of treatment. Studies analyzing any new depigmenting agent compare it to hydroquinone. Choosing which product to utilize is dependent upon several factors: Fitzpatrick skin type, skin sensitivity and color, allergies, sun exposure, comorbid conditions, patient preference, and cost. Combination therapy seems to be advantageous as various compounds can act upon different steps in the pigmentation pathway [5,6]. Crucial to the treatment of hyperpigmentation and hyperpigmented lesions is counseling the patient on realistic expectations and the need for diligent treatment. Proper sun protection, as always, is paramount.

Conflicts of interest statement

M.Rendon: Clinical trials as main (head) clinical or laboratory investigator, or study coordinator (Galderma, Pierre Fabre, Johnson & Johnson, Mary Kay Cosmetics, Obagi Medical products); Clinical trials as co-investigator or study contributor (Galderma, Pierre Fabre, Johnson & Johnson, Mary Kay Cosmetics, Obagi Medical products); occasional involvements: expert reports (L'Oréal, Merz, Allergan, Pierre Fabre, Procter & Gamble, Mary Kay Cosmetics, Obagi Medical products); occasional involvements: advisory services (Galderma, L'Oréal, La Roche Posey, Johnson & Johnson, Merz, Allergan, Pierre Fabre, Mary Kay Cosmetics, Obagi Medical products); conferences: attendance as contributor (Galderma, L'Oréal, La Roche Posay, Johnson & Johnson, Merz, Allergan, Procter & Gamble, Neostrata); conferences attendance as audience member (Galderma, L'Oréal, La Roche Posay, Johnson & Johnson, Merz, Allergan, Procter & Gamble, Neostrata).

S.M.H.

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Lasers

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KEYWORDS
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Summary
Lasers are a very effective approach for treating many hyperpigmented lesions. They are the gold standard treatment for actinic lentigos and dermal hypermelanocytosis, such as Ota nevus. Becker nevus, hyperpigmented mosaicisms, and lentigines can also be succesfully treated with lasers, but they could be less effective and relapses can be observed. However, lasers cannot be proposed for all types of hyperpigmentation. Thus, freckles and café-au-lait macules should not be treated as the relapses are nearly constant. Due to its complex pathophysiology, melasma has a special place in hyperpigmented dermatoses. Q-switched lasers (using standard parameters or low fluency) should not be used because of consistent relapses and the high risk of post-inflammatory hyperpigmentation. Paradoxically, targeting the vascular component of the melasma lesion with lasers could have a beneficial effect. However, these results have yet to be confirmed. In all cases, a precise diagnosis of the type of hyperpigmentation is mandatory before any laser treatment, and the limits and the potential side effects of the treatment must be clearly explained to patients.

MOTS CLÉS
Lasers ;
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Naevus de Ota ;
Mélasma

Résumé
Les approches lasers permettent aujourd'hui de traiter efficacement un grand nombre de lésions hyperpigmentées. Les lasers sont le traitement de référence des lentigos actiniques et des hypermélanocytoses dermiques comme le nævus de Ota. L'indication d'un traitement laser devra être discutée pour d'autres situations telles que les naevus de Becker, les mosaïcismes pigmentaires ou les lentigines, en raison d'une efficacité plus inconstante et du risque de récidive. Les lasers pigmentaires ne sont toutefois pas la réponse à tous les troubles pigmentaires. Ainsi les éphélides et les taches café-au-lait ne devront pas être traitées en raison d'un risque de récidive quasi constant. Par sa physiopathologie complexe, le mélasma occupe une place à part. Les lasers déclenchés (en paramètres standard ou à faibles fluences) ne devront pas être utilisés car les récidives

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sont constantes et les risques d'aggravation loin d'être négligeables. Paradoxalement, l'utilisation d'un laser pour cibler la composante vasculaire du mélasma semble avoir un effet bénéfique mais qui nécessite encore d'être confirmé. Dans tous les cas, un diagnostic précis du type d'hyperpigmentation est indispensable avant tout traitement, et les limites du traitement ainsi que les effets secondaires possibles devront être clairement expliqués au patient.

Introduction

The development of lasers has resulted in considerable progress in the treatment of cutaneous hyperpigmentations. However, hyperpigmented lesions come in many varieties and form a highly heterogeneous group. They can result from quantitative or qualitative anomalies of melanic pigments (eumelanin and pheomelanin), epidermic melanocyte proliferation, or the abnormal presence of melanocytes in the dermis. They also sometimes occur secondary to an abnormal increase in other endogenous pigments (bilirubin, iron, etc.) or exogenous pigment deposits (heavy metals, tattoos, cosmetics, etc.). The responses of these different pigmentary disorders to laser treatment vary considerably and a precise diagnosis is indispensable to determine the pertinence of laser treatment and to guide the choice of parameters to the greatest advantage.

Principles of pigment lasers

The general principle of pigment lasers is based on selective photothermolysis [1]. To obtain a selective action, the laser pulse duration must be at least ten times less long than the target's thermal relaxation time. The thermal relaxation time is the time necessary for a target to lose half of the temperature acquired following the laser shot. This time is proportional to the size of the target (but also varies to a lesser degree depending on its shape and thermal diffusivity). For melanin pigmentary disorders, the laser target is the melanosome. This is an organelle specific to melanocytes, close to lysosomes, within which melanin is produced. Melanin is the chromophore targeted by the laser treatment. It is important to know that two types of melanin are produced within melanosomes: eumelanins, a brownish-black photoprotective pigment, and pheomelanins, a nonphotoprotective brownish-red pigment. The difference in color of these melanins explains the absorption curve in relation to the light wavelength, which differs between the two. This curve is displaced toward the left for the pheomelanin, which explains that lesions with a high content in pheomelanin such as ephelides or actinic lentigines, when they are very light in color (notably in individuals with a light phototype) are best treated with Q-switched 532-nm laser pulses. Most other pigmentary lesions contain more eumelanin and are generally better targeted by 694- or 755-nm wavelengths. As they mature, melanosomes are loaded in melanin and then are distributed to the adjacent keratinocytes [2]. A melanosome measures approximately 1 μm. Its relaxation time varies from 1 to 10 μs on average. The laser pulse duration should therefore be less than 100 ns. The size of most of the other pigments is much the same, which means that the same pulse durations can be used. Thus, the lasers used in pigment pathology are Q-switched, with emission duration generally varying between 10 and 100 ns [3].

Depending on the type of pigment disorder, the increase in pigmentation can be caused by an increase in intraepidermic melanin (epidermal hypermelanosis), an increase in the number of epidermal melanocytes (epidermal hypermelanocytosis) or dermal melanocytes (dermal hypermelanocytosis) or the abnormal presence of melanin in the dermis (dermal hypermelanosis or pigmentary incontinence). The disposition of pigment in the dermis or the epidermis guides, in part, the choice of the wavelength. Thus, dermal pigmentations are mainly treated with 1064-nm Nd: YAG lasers whose wavelength penetrates more deeply in cutaneous tissue. These same lasers are also preferred to treat individuals with a dark phototype because they interact less with the melanin contained in the superficial layers of the epidermis. The type of pigment should also be taken into account. The color of the lesion and the patient's phototype can be assessed by the clinician to evaluate the pheomelanin / eumelanin ratio.

The main pigment lasers are therefore the Q-switched Nd: YAG lasers, 1064 nm and 532 nm when they are doubled in frequency, the 694-nm ruby laser, and the 755-nm alexandrite laser. These wavelengths provide good absorption by melanin pigments and less absorption by hemoglobin, which is the other major chromophore of the skin. It is also sometimes possible to use ablative lasers, which target water. In all the water-containing cells, these lasers are not selective and lead to destruction of all the cells. Used in a fractionated mode, they are essentially used in the treatment of melasma and to a lesser degree actinic lentigines.

Ota nevus and acquired dermal hypermelanocytosis

Ota nevus corresponds to dermal hypermelanocytosis of the periorbital area observed most often in subjects of Asian

ethnic descent. The melanocytes are located in the reticular and papillary dermis. The epidermis is normal. Ruby, alexandrite, and Nd: YAG Q-switched lasers have all demonstrated their efficacy in this indication. The pigment depth favors the use of lasers with high wavelengths. A comparative between 755-nm alexandrite lasers and 1064-nm Nd: YAG lasers seems to confirm this hypothesis by showing the superiority of 1064-nm Nd: YAG laser in terms of efficacy (the side effects were similar with the two lasers) [4]. It is advised that two sessions be spaced 2 months apart. The laser treatment of Ota nevus in children provides better results and a lower number of complications than the same treatment undertaken in the adult subject [5]. The color of the pigmentation is also an important predictive factor of the response to treatment. Blue-gray lesions decrease on average at least 75% in six sessions, whereas browner pigmentations require half as many sessions to achieve the same result [6]. In addition, several cases suggest that relapses after treatment may be more frequent than previously thought [7]. This risk should therefore be clearly explained to the patient and his or her parents before any treatment. Finally, the occurrence of melanoma with Ota nevus has already been reported, which urges surveillance of treated patients.

Ito nevus (congenital dermal hypermelanocytosis involving the clavicle, the deltoid, or the scapular region) and the other congenital forms of dermal hypermelanocytosis can also be successfully treated with Q-switched laser. Here again 1064-nm Nd: YAG laser should be preferred.

Acquired dermal hypermelanocytosis is poorly known but is not exceptional. The clinical picture is the same as congenital dermal hypermelanocytosis but with late onset, generally during the second or third decade. No data have been reported in the literature, but in our experience, these lesions also respond to Q-switched 1064- or 755-nm lasers with fewer sessions compared to the congenital forms (Fig. 1). When they are located on the face, they can be confused with melasma or a postinflammatory pigmentation. It is therefore very important to know how to recognize them because a laser approach in these cases can considerably improve the lesions.

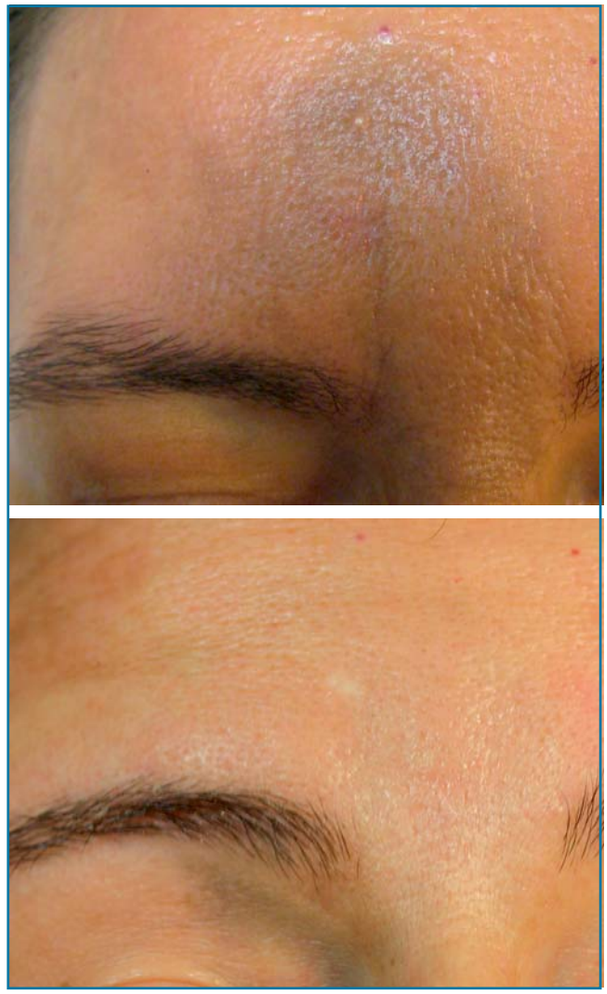

Figure 1. Acquired dermal hypermelanocytosis of the face. (a) Before treatment. (b) After four sessions of Q-switched 1064-nm laser.

Actinic lentigines

Q-switched lasers at 755, 694, and 532 nm are consistently effective in one or two sessions [8]. The efficacy of laser treatment of actinic lentigines is superior to that of cryotherapy, even if the latter is less expensive [9]. The lightest-colored actinic lentigines respond the best to 532-nm Q-switched Nd: YAG. The slightest doubt should lead to biopsying an atypical lentiginous lesion so that a possible lentigo maligna melanoma is not missed. More recently, fractionated thulium fiber laser has been shown to improve actinic lentigo lesions [10]. This laser emits a 1927-nm wavelength that has a strong affinity for water. Unlike Q-switched lasers that effectively but selectively treat actinic lentigines, the fractionated thulium laser approach plays a greater role in photoaging treatment in its globality.

Lentigines and ephelides

Pigment lasers have shown their efficacy in the treatment of lentiginous lesions, including when these lesions are labial with systemic involvement such as in Peutz-Jeghers-Touraine syndrome [11]. The lentigines disappear in one or two sessions. It is important to remember here that before proposing lentigo treatment, one must ensure that these lesions are not part of a more complex disease with extracutaneous manifestations.

Ephelides can also be effectively treated with laser. However, relapses are nearly certain and greatly limit the advantages of this approach. Given the strong component in pheomelanin of ephelides, the wavelength choice should preferably be toward 532 nm.

Café-au-lait spots

Café-au-lait spots can be treated with a number of pigment lasers. The response of café-au-lait spots to these different lasers is variable. No laser has shown superior results and comparative studies are still needed. No correlation has been demonstrated between the clinical or histological aspect of café-au-lait spots and their response to treatment [12]. Unfortunately, relapses are very frequent and the patient should be clearly informed. Therefore, before treating large café-au-lait spots, it is advisable to treat a test zone and see the patient after a summer season to judge the efficacy and stability of the response.

Nevus spilus

Several pigment lasers, notably Q-switched ruby and alexandrite lasers, have demonstrated their efficacy in the treatment of nevus spilus [13,14]. As for café-au-lait spots, aggravation or relapse can be observed after treatment. In addition, the risk of developing melanoma on this type of lesion, although rare, is real. Therefore, laser treatment should be proposed with the greatest of precautions and a biopsy should be done before treatment if the clinical aspect is atypical.

Congenital nevus

Other than the risk of melanoma onset, congenital nevus presents a major esthetic prejudice when they are large. Several types of laser approaches have been proposed when surgical treatment was impossible. Nonselective destruction using CO_2 laser or Er: YAG laser sometimes combined with pigment laser can provide a clear reduction of the pigmentation with sometimes prolonged effects lasting several years [15]. The results of this approach are unfortunately impermanent and scarring is often pronounced.

The selective destruction of pigment using Q-switched ruby, alexandrite or Nd: YAG laser sometimes provides a significant decrease in pigmentation, hairs, and even improvement of cutaneous texture [16]. However, often partial repigmentation is frequent and histological studies confirm the persistence of nevocytes, notably dermal, after laser treatment. More importantly, the long-term effect of laser energy on these lesions and the potential role played by the fibrosis thus triggered on the secondary development of melanoma is currently unknown. Encouraging results have been obtained with Q-switched ruby laser using progressively increasing doses and sessions begun very early at 1 month of age and then pursued every 2 weeks for 2–3 months [17]. Eight children out of nine had a response deemed good to excellent at the 1-year follow-up. These results should be confirmed on larger numbers of patients and with a longer follow-up. In the meantime, laser treatment of congenital nevi should be considered with the greatest caution and discussed on a case-by-case basis with the parents, weighing the advantages as well as the risk of each technique. Whatever approach is chosen the children should be closely monitored.

Becker nevus

The pilary component of Becker nevi generally responds very well to depilatory laser treatment. The pigment component can also be treated with laser but it is not rare to observe relapses after treatment. Here again it is prudent to test a zone before treating large surfaces. Most authors recommend beginning by treating the pilary component; however, it has never been proven that this reduces relapses when hyperpigmentation is treated thereafter. Therefore, the order of treatment of hypertrichosis and hyperpigmentation does not play a role in the final result. The choice depends most particularly on the aspect of the hamartoma and each patient's request.

Pigmentary mosaicism

The data on the laser treatment of pigmentary mosaicism are nearly nonexistent. Because of the heterogeneity of these mosaicisms and the differences in treatment responses that we have observed in our patients, we systematically propose a test session with different wavelengths. Relapses are not rare, but they are not constant and esthetically satisfactory results can be obtained (Fig. 2).

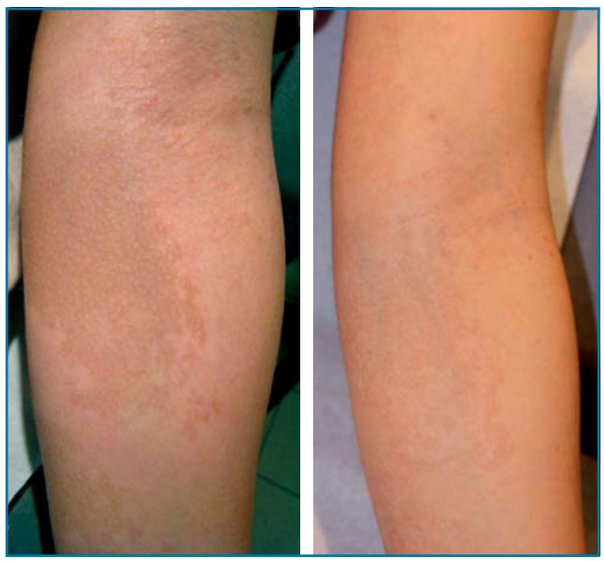

Figure 2. Pigmentary mosaicism of the arm. (a) Before treatment. (b) After two sessions of Q-switched 755-nm alexandrite laser treatment.

Melasma

Although relatively frequent and often a source of therapeutic demand, melasma is not a good indication for Q-switched laser. Although it frequently reduces hyperpigmentation, its efficacy is always transitory and postinflammatory hyperpigmentations are very frequent [2]. Recently, small series have reported the efficacy of 1064-nm Nd: YAG using low fluency levels below the photothermolysis threshold. These results were unfortunately not confirmed by a randomized prospective study of the hemiface that compared hydroquinone 2% versus hydroquinone 2% associated with low-fluency 1064-nm Nd: YAG laser. Despite a considerable improvement at the end of treatment in the laser group, all the lesions recurred 12 weeks after the end of treatment and postinflammatory hyperpigmentations were noted in nearly 20% of the cases [18].

A few interesting results have been reported with pulsed light lamps, but the level of evidence is clearly insufficient to propose this treatment, at least in first-line therapy [19,20].

Fractional nonablative lasers have also been used in the treatment of melasma with encouraging initial results [21,22]. An open clinical study but with a 6-month follow-up period using 1550-nm nonablative fractionated laser showed, after four sessions spaced 1 month apart, improvement qualified as pronounced in 24% of the patients [23]. However, after 6 months, a moderate relapse was noted in these patients with final improvement that remained statistically significant but clinically moderate. It is important to note that 13% of the patients experienced an aggravation of their hyperpigmentation. A prospective randomized study showed that at 6 months this laser approach was not better than photoprotection alone [24].

The data with fractionated ablative lasers (CO_2 or erbium) are even more limited. As is frequent, the first cases reported seemed to give encouraging results, but it is too early to propose these lasers in daily practice. However, other than their specific effects, these lasers create micro-pits that could also be used to increase the penetration of topical blanching creams and potentiate their action. The only study available indeed suggests a synergetic effect of fractionated CO_2 laser with a depigmenting triple combination [25]. Unpublished data obtained in our department show similar results and underscore the potential value of this type of approach in cases of melasma resistant to the depigmenting triple combination cream. Unfortunately, this approach does not prevent relapse.

Fractionated thulium laser has recently shown efficacy in a pilot study [26]. The results were modest, however, and significant only at 1 month. Complementary studies are therefore clearly needed to determine the real value of this laser in the treatment of melasma.

Today, none of these laser approaches has shown superiority compared to the Kligman triple combination cream, which must remain the reference first-line treatment [27]. However, it was clearly demonstrated that melasma lesions also include an increase in vascularization. By targeting the vascular component of melasma with a pulsed-dye laser (PDL), a prospective, comparative, intraindividual study showed that the association of PDL and Kligman triple combination cream was significantly superior to the triple combination cream alone [28]. It is interesting to note that relapses after a summer of follow-up were significantly less on the side treated with PDL. A study with another laser targeting the vascular component of melasma also noted a beneficial effect [29]. These preliminary data must be confirmed but emphasize the potential value of targeting the vascular component of melasma.

Periorbital dark circles

This term often encompasses a heterogeneous group of disorders that lead to darkening around the suborbital area. This darkening can be pigmentary in origin but also vascular or caused by a loss of subcutaneous fat. True melanic pigmentary circles can be treated by Q-switched lasers as well as intense pulsed light [30,31]. However, the data are limited with inconsistent results.

Ochre dermatitis and other hemosiderin deposits

The peak of hemosiderin absorption is between 410 and 415 nm. The use of short wavelengths is therefore preferable. The data reported in the literature are limited. Ochre dermatitis has been treated by intense pulsed light source [32]. Deposits of hemosiderin as sequelae of Kaposi lesions have also been effectively treated by Q-switched 755- and 532-nm laser [33].

Drug-induced pigmentation

Certain drug-induced pigmentations (such as tetracyclins, synthetic antimalarials, or amiodarone) can be effectively treated with Q-switched lasers [34-36]. The pigmentation is dermal and 694-nm ruby, 755-nm alexandrite, and most particularly 1064-nm Nd: YAG lasers are preferable to 532-nm Nd: YAG laser.

Pigmented seborrheic keratosis and dermatosis papulosa nigra

Beginning flat pigmented seborrheic keratosis can be treated with Q-switched laser [37]. Ablative CO_2 or erbium lasers can also be used to treat seborrheic keratosis as well as dermatosis papulosa nigra lesions (Fig. 3) [38].

Postinflammatory pigmentations

Postinflammatory pigmentations are secondary to pigment incontinence and generally are not good indications for laser treatments. On the contrary, these can lead to increasing the pigmentation consecutive to transitory inflammation instigated by the laser shot.

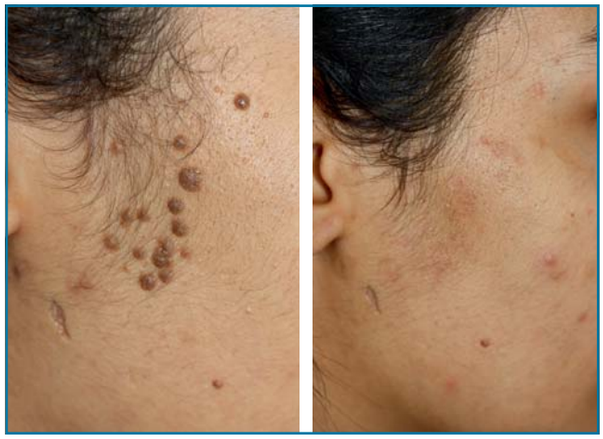

Figure 3. Dermatosis papulosa nigra. (a) Before treatment. (b) One month after one session of erbium laser dermabrasion. **a** | **b**

Side effects

Postinflammatory pigmentations are the most frequent complication. They are encountered for the most part in patients with phototypes III, IV, and V. Rigorous photoprotection should be recommended after a laser session and treatments during the summer season should be proscribed for any lesions located in a particularly photoexposed area. These postinflammatory pigmentations generally regress in a few weeks to a few months. Topical steroid applications, whether or not associated with hydroquinone, can sometimes be useful. The risks of hypochromia are low. They are generally transitory but prolonged hypochromic sequelae have been described, essentially with ruby 694-nm lasers. Scar lesions are rare and generally result from the use of excessively high fluencies.

Conclusion

Pigment lasers show remarkably high performance in certain pigmentary disorders, but they can be ineffective if not harmful in others. Tolerance is generally good and the side effects limited. The risks are not exceptional, however, and the dermatologist should be aware of them. In all cases, a rigorous semiological approach is necessary and the advantages as well as the risks of the treatment should be clearly explained to patients, who still often consider laser to be a miracle treatment for all pigmented lesions.

Conflicts of interest statement

T. Passeron: None

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Dermocosmetic management of hyperpigmentations

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KEYWORDS
Hyperpigmentations,
Sun lentigines,
Melasma,
Dermocosmetics,
Depigmenting agents

Summary
Hyperpigmentations are very frequent situations that can have considerable impact on the quality of life of affected individuals. However, even if the esthetic prejudice they generate is undeniable, lentigo and melasma are benign conditions that require above all a risk-free management.
In addition to the dermatological procedures (peeling, laser, etc.) and the topical drugs available to the dermatologist, there remains significant room for depigmenting dermocosmetic products. These products succeeded to transpose features of the classic pharmaceutical formula invented by Kligman from which they were inspired to the field of dermocosmetics. They comprise activators of epidermal turn-over, skin exfoliants, and active ingredients that interfere with the different stages of melanogenesis, without having the side effects of hydroquinone whose usage remains limited to the field of prescription drugs. Antioxidants are a particularly interesting addition because they participate in reducing cutaneous inflammation and efficiently complete the action of the other components of a depigmenting formula.
It is important to remind the aggravating role that sun exposure has on hyperpigmentations. Therefore, measures of rigorous photoprotection are mandatory. Medical makeup, transitory or definite, is an interesting option for the management of hyperpigmentations. Consequently, depigmenting dermocosmetics, used in monotherapy but - most frequently - in combination with dermatological procedures, can be used in literally all types of hyperpigmentations with an efficacy that is dependent on the specific etiology. They are suited to be part of a treatment program that has to be adapted on a case-by-case basis.

MOTS CLÉS
Hyperpigmentations ;
Lentigos solaires ;
Melasma ;

Résumé
Les hyperpigmentations sont des situations très fréquentes qui vont pénaliser la qualité de vie des personnes qui en sont atteintes. Cependant, si lentigos et mélasma constituent un indéniable désagrément esthétique, leur caractère tout à fait bénin impose une prise en charge dénuée de risques significatifs.
A côté des procédures (laser, peeling...) et des topiques médicamenteux dépigmentants dont dispose le dermatologue, il reste une large place pour les dépigmentants dermo-

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Dermocosmétiques ;
Depigmentants

cosmétiques. Ces derniers vont s'inspirer des mécanismes d'action du classique « trio de Kligman » (médicamenteux) et en réaliser une transposition dermocosmétique incluant des accélérateurs du turn-over épidermique, des exfoliants, et des actifs agissant aux différentes étapes de la mélanogénèse, sans posséder les effets secondaires de l'hydroquinone, limitée aujourd'hui à une utilisation médicamenteuse. Une place particulière doit être faite pour certains antioxydants qui participent à la réduction de l'inflammation cutanée et complètent efficacement l'action des autres familles d'actifs.
On ne saurait trop rappeler le rôle aggravant constant de l'exposition solaire et la nécessité de mettre en place des mesures systématiques de photoprotection. Le maquillage médical correcteur restant le recours, transitoire ou définitif, à la prise en charge des hyperpigmentations.
Ainsi, les dermo-cosmétiques dépigmentants pourront être utilisés pour quasiment tous les types d'hyperpigmentations, avec une efficacité très variable selon leur étiologie, seuls mais le plus souvent en combinaison avec des procédures, participant ainsi à un véritable programme de soin qu'il faudra idéalement adapter au cas par cas.

Introduction

Hyperpigmentations are very frequent situations that can have considerable repercussions on the socioprofessional life of the individuals concerned, the majority within the female population.
Consequently, there is great demand for improvements calling on dermatological procedures (peeling, laser, etc.), topical drugs, as well as a wide palette of dermocosmetics claiming depigmenting activity.
It should be remembered that hyperpigmentation clearly generates esthetic damage, with a subjective experience that varies greatly from one individual to another, but these disorders are of a benign nature. Management of the condition should disregard any excessive act or application of topical medications with notable side effects. Despite this observation, outside the authorized markets one can find a large number of preparations with no more than a cosmetic name, using cytotoxic depigmenting agents and high-concentration steroids, a situation that raises grave concerns.
Contrary to this approach, a certain fatalism can be observed concerning hyperpigmentations. This is in large part related to the inefficacy – perceived as such by users – of a large number of depigmenting agents with lofty claims on paper but mitigated results in practice.

Generalizations about hyperpigmentations

The main hyperpigmentations encountered in dermatological practice are melasma, lentigines, pigmented scars, postinflammatory pigmentations, and Berloque dermatitis.

Attenuating, or even better, eradicating these hyperpigmentations requires the systematic use of an external photoreceptor.

Elimination of the cause of the hyperpigmentation, when possible, should obviously be attempted: although this goes without saying for Berloque dermatitis, it becomes more complex when it involves giving up oral contraception.

To fight against persistent hyperpigmentation, the dermatologist can call on physical and chemical procedures (laser, cryotherapy, peeling, etc) for lentigines but will generally prefer topical treatments for diffuse hyperpigmentations, including melasma. This is a very general framework, with the choice of techniques related to each individual situation and remaining highly operator-dependent. Very frequently, it is a combination of several approaches (procedures + topical medications) that will be proposed in the end [1].

External photoprotection

External photoprotection is fundamental to the hope of improving a hyperpigmentation, whatever the etiology may be. Sun exposure always plays an aggravating role, considerably reinforcing hyperpigmentations already present and facilitating the appearance of new brown areas [2-4].

Therefore, daily use of a high-index photoprotector, from the high-protection SPF50+ products, is systematically proposed. This measure does not obviate the need for adopting a lifestyle that will reduce sun exposure.

In winter periods more generally when there is little sun, it will be possible to reduce this photoprotection to the application of day creams with photoprotection incorporated (SPF 20 or 30).

Sun protection is also of major importance following dermatological procedures, when the risk of postinflammatory hyperpigmentation is particularly high. The highest protection indices should be chosen but in this specific situation on a recently lesioned skin, one should also select textures that are easily spread on the skin, providing comfort, with optimal tolerance (simple formulas, limited number of filters and screens).

Depigmenting dermocosmetics

Broadly speaking, the efficacy of a depigmenting agent can manifest in three ways:

- by accelerating the epidermic turnover and creating superficial exfoliation, which will facilitate the elimination of keratinocytes loaded in pigments as well as surface squames increasing the hyperpigmentation aspect, particularly in cases of senile lentigines;
- by acting at the different stages of melanogenesis: synthesis of melanin by the melanocyte, then distribution of the pigment to the keratinocytes, and finally the process of destruction of this pigment;
- by acting on any inflammatory component of the hyperpigmentation and reducing the intrinsic pro-inflammatory risk of the active depigmenting and exfoliating ingredients that are often associated.

Optimal management of hyperpigmentations ideally includes an association of several active agents acting on the three above-mentioned components. With this in mind, Albert Kligman was the first to develop the famous "depigmenting trio" combining in the same formulation retinoic acid, hydroquinone, and dexamethasone. This preparation, in its original aspect or through its many adaptations, remains the reference drug in the topical treatment of hyperpigmentations, with, however, its limitations: irritation induced by retinoic acid, problems related to the toxicity of hydroquinone, and its potential side effects inherent to any local corticosteroid therapy.

Retinoic acid and dexamethasone are no longer within the realm of dermocosmetics and remain strictly limited to medical prescription. Hydroquinone is more complex. This is a phenolic by-product whose depigmenting action is perfectly documented. Long used in dermocosmetics at concentrations ranging from 2 to 5%, the product has progressively been removed from the non-medicinal market, and since 2001 has been totally banned in dermocosmetics in European countries, a decision justified by the risk of distant depigmentation, cases of ochronosis, and a cytotoxic and potentially mutagenic mechanism of action, all of which make this active agent incompatible with the cosmetic status.

The manufacturers therefore turned toward other depigmenting active agents, more reliable but much less effective. In the spirit of the Kligman trio, several associations have been developed: a combination of exfoliant, depigmenting agent, and sunscreen or a replacement in these nonmedicinal trios of the anti-inflammatory active agent with anti-free-radical molecules that can potentiate the depigmenting effect [5].

Dermocosmetic active agents with an exfoliant and depigmenting potential

These are nonmedicinal molecules improving the epidermal turnover, certain of which have a specific depigmenting action.

The following can be cited:

- *Glycolic acid* (and more generally the alpha-hydroxyacid family) used in topical applications, particularly for its keratolytic and exfoliative properties. There are a number of formulas incorporating 10 or 15% of this active agent. At a high concentration, glycolic acid is the main ingredient in chemical peelings.
- *Beta-hydroxyacids*, with a low concentration of salicylic acid, are also found in certain depigmenting formulations.
- *Retinoids* can act at several levels of the synthesis and release of melanin, but it is most particularly their role in epidermal regeneration that is highlighted. Without tretinoin, not authorized in cosmetics, its precursors can be used: retinol, but most particularly retinaldehyde, which has good cutaneous tolerance. The additional advantage of retinoids is their well-documented effect on all of the processes involved in aging of the skin, processes potentially involving hyperpigmentation.

Depigmenting and anti-free-radical dermocosmetic active agents

This is a highly diverse category of substances that claims an action on the synthesis and/or transfer of melanin, most often by inhibition of tyrosinases or an action on the dendricity of melanocytes, one of the processes responsible for the vectorization of pigment toward keratinocytes.

The list of these dermocosmetic ingredients is not exhaustive. Moreover, it cannot have a universal definition because depending on the legislation in the different countries, the concentrations, and the type of formulation, one can find cosmetic depigmenting agents in free use, authorized for use or prohibited depending on their concentration, with a different status depending on the concentration (cosmetic or "quasi-drug" as in Japan), even banned by some highly restrictive legislation. The issues underlying these variations in regulations is essentially related to its metabolism deemed too close to that of hydroquinone on the stages of melanogenesis.

- *Azelaic acid* is a saturated dicarboxylic acid, which has been demonstrated in cultures of *Malassezia furfur* and which may be responsible for the dyschromia of pityriasis versicolor. It inhibits tyrosinase *in vitro* and acts only on hyperactive melanocytes, producing no adverse depigmenting effect on normal areas. Used at the 20% concentration, azelaic acid has been positioned both as a cosmetic and as a medication (depigmentation, acne, rosacea).
- *Kojic acid* is an organic compound extracted from *Aspergillus* fungi. It is said to act on tyrosinase and also has an anti-inflammatory and antioxidant effect through chelation of copper necessary for the synthesis of melanin. Kojic acid is very widely used and is found incorporated in a number of dermocosmetic products.
- *Stabilized vitamin C* also has an inhibiting action on tyrosinase and is probably the dermocosmetic ingredient the most frequently used in controlling pigmentary disorders. It can be found at different concentrations in two groups of products: depigmenting agents as well as whitening agents, a highly valued dermocosmetic category in Asian countries, which aims more at homogenizing and lightening the color of the skin than at erasing established hyperpigmentations.
- *Resorcinol, rucinol, resveratrol, SymWhite 377, and myrtle extract* are found in dermocosmetic formulations

claiming to have an action on the synthesis of melanin and its transfer. We should also cite *glabridine* (licorice extract), *arbutin*, and plant extracts known for their high flavonoid content.
- Amongst the group of anti-inflammatory and anti-free-radical agents, several drugs and plant extracts claim to have a direct or indirect depigmenting effect through action on the inflammatory cascade by blocking free radicals: *selenium, vitamin E, pre-tocopheryl, niacinamide, green tea, Aloe vera, soy*, etc.

Most of the available dermocosmetics include the association of two or three of these substances, with possibly a sunscreen in the formulation [6].

Indications

Depigmenting dermocosmetics can be used with no notable disadvantages on all types of pigmentation. The limiting stage is the level of efficacy that can be expected. In all cases, a significant result will require a prolonged use and association of photoprotection measures.

In practice, dermocosmetics could be a back-up to dermatologic procedures, either before an intervention to limit the surfaces to be treated or post-procedure for an optimal homogenization of tone. This last point is particularly useful for circumscribed hyperpigmentations.

They are found most often in exclusive use on scattered pigmentations such as melasma, for which dermatological procedures do not always lead to satisfaction.

Correction with medical makeup

Medical makeup is the last resort for depigmenting treatment failures and is most particularly a palliative solution for patients during treatment. Medical makeup is essentially based on the complementarity of colors and their neutralization (color circle). Particular attention should be paid to the quality of the textures and their tolerance.

Conclusion

Frequently an unsightly annoyance, hyperpigmentations are approached through dermatological procedures and depigmenting medicinal preparations completed by a wide range of dermocosmetics. Because of their status, the latter should guarantee good tolerance and be perfectly innocuous. This is a difficult challenge if a significant level of efficacy is desired as well as clear differentiation from hydroquinone, a long time reference product and today no longer part of dermocosmetics, and if legislation of the different countries is to be respected, the standardization of which is far from acquired. Despite these restrictions, depigmenting dermocosmetics are in full expansion given the important place they occupy in the overall management of hyperpigmentations.

Conflicts of interest statement

D. Guerrero: Employee of Pierre Fabre Group.

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Medical makeup: the correction of hyperpigmentation disorders

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KEYWORDS
Medical makeup;
Correction;
Hyperpigmentation;
Coral concealer

Summary
Medical makeup corrects skin tone imperfections with dermocosmetic products, which bring together tolerance efficacy, colour neutralization and sun protection.
Highly suitable for imperfections caused by hyperpigmentation, it allows patients affected by these disorders to cover them up effectively and discretely, giving them a better quality of life.

MOTS CLÉS
Maquillage médical ;
Correction ;
Hyperpigmentation ;
Correcteur corail

Résumé
Le maquillage médical corrige les imperfections du teint avec des produits dermocosmétiques, qui allient tolérance, efficacité, correction par la couleur et protection solaire.
Très adapté aux troubles de l'hyperpigmentation, il permet aux patients affectés par ces défauts cutanés, de les masquer avec efficacité et discrétion, améliorant ainsi leur qualité de vie.

Correspondence.
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Introduction

Although the objective of cosmetics is to enhance one's beauty while adhering to the codes of fashion, the goal of medical makeup is relatively distant from this use.

In following trends to an excess, it is possible to highlight what one wishes to hide: it is not rare to see women with accentuated lines and wrinkles because of excessive use of foundation and eye shadow.

This is also the case on heavily made-up acne skin: the skin looks pock-marked. As for colored cutaneous defects, after application of makeup they may appear like a mask, which is no less satisfactory.

Therefore, to correct dermatological imperfections, the criteria that should be taken into account are above all the symptoms, the medical prescription (should a sunscreen be applied, are there any allergies to cosmetics, etc.) and the patients' tastes and habits.

Medical makeup techniques can mask these cutaneous imperfections effectively and naturally, with no risk of worsening dermatological disorders [1,2].

The positive psychological effects for patients have long been well known [3] and improvement on the Dermatology Life Quality Index (DLQI), the quality-of-life assessment scale for dermatology patients, has been proven [4].

Basic principles of medical makeup

Color correction

Severe imperfections are difficult to hide without risking a "mask" effect. To effectively but naturally correct them, it is necessary to use color correction. This correction is well known in medical makeup.

As can be observed on the chromatic circle (Fig. 1), showing all of the complementary colors:

- green is the opposite color of red,
- yellow is the opposite color of blue.

Mixed together, the opposite colors are neutralized. With this technique, it is possible to apply less foundation and thus obtain a lighter and more natural makeup.

Green neutralizes red: rosacea, scars, psoriasis …(Fig. 2)

Yellow neutralizes blue-violet: bruises, angioma, varicose veins … (Fig. 3)

Correction of brown imperfections is made possible by the color values.

"Value" indicates the brightness defining the colors: each color can have a light or dark aspect. This requires adding white or black (see example with the color orange, (Fig 4) [5].

For this reason, the application of a beige foundation directly on a brown hyperpigmentation leaves a grey reflection (Fig. 5).

While the imperfection is neutralized by adding an orange corrector, the grey aspect disappears (Fig. 6).

Coral neutralizes brown: chloasma, melasma, lentigo, hyperpigmented scars.

Figure 1. Chromatic circle.

Makeup bases

The indispensable step before correcting a cutaneous imperfection is the application of a makeup base: the texture of a daytime cream is perfectly adapted. With no skin hydration, the pigments contained in the makeup attach to the reliefs in the skin (squames, excoriated papules, fine lines, etc.) and highlight them [6].

Complexion

In dermatology, makeup products must be hypoallergenic, non-comedogenic, have a strong concealing power so that as little is applied to the skin as possible, be resistant to transpiration, and have very good wear qualities so that it does not have to be reapplied during the day.

Correctors

Correctors are the first step in correcting severe and colored imperfections; they will always be followed by a foundation to unify the complexion.

After application, the lesion becomes light grey and then it is possible to apply a small amount of foundation and thus avoid the mask effect.

Compact foundations

With their very high concentration in pigments, these compact foundations provide rapid and effective correction. In addition, their wear is superior to fluid foundations and they do not require reapplication during the day.

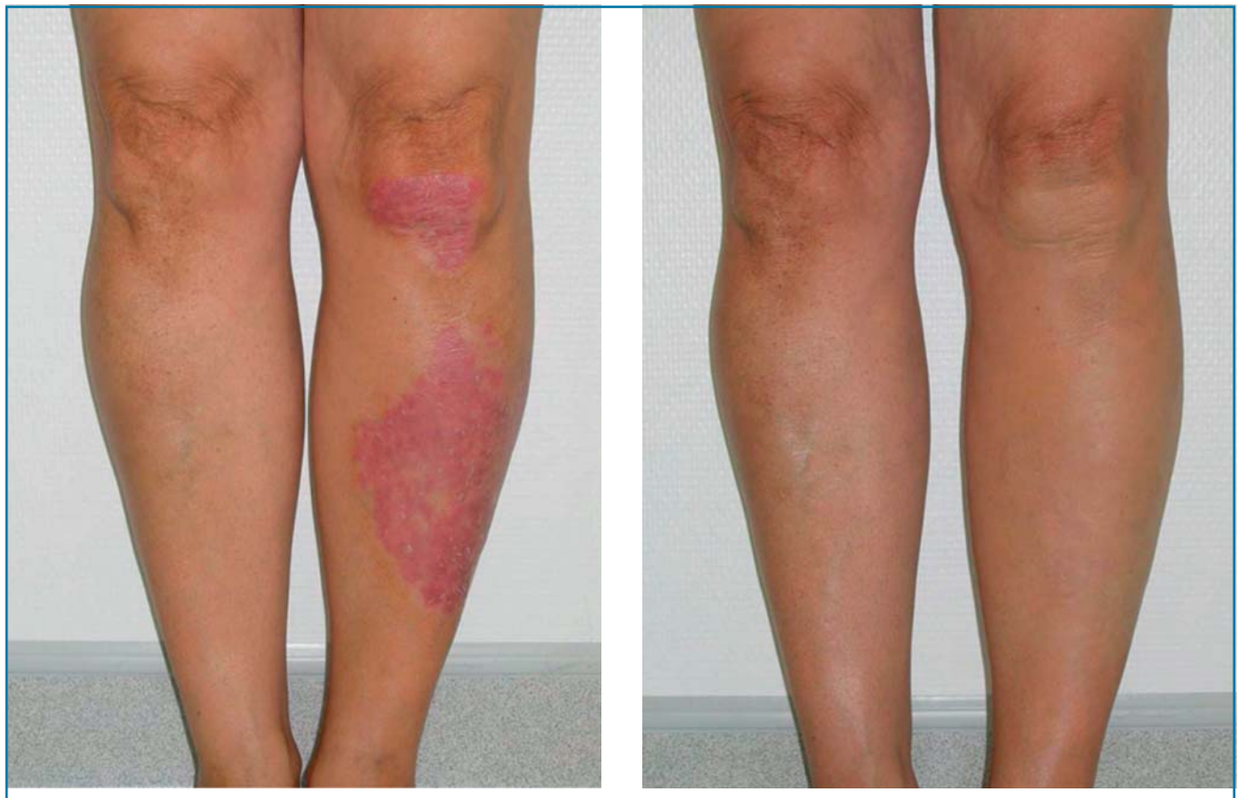

Figure 2. Correction of psoriasis lesions with green cover stick and compact foundation cream.

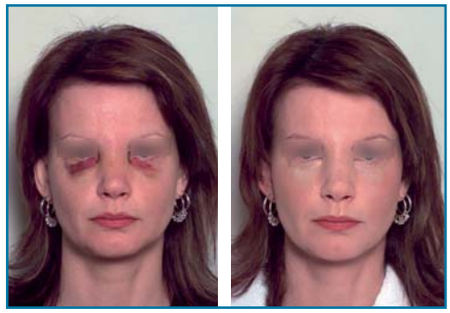

Figure 3. Bruising post rhinoplasty correction with yellow cover stick and compact foundation cream.

Foundations colors

Foundation colors are obtained by mixing iron oxide – black, brown, red, and yellow – and with a unifying effect achieved by adding titanium.

Simply speaking, white, brown, and black are needed to adapt to all complexions, then yellow to provide luminosity and pink to add freshness to the complexion.

Two foundation colors exist: the pinks and the yellows.

The pink colors are better adapted to light phototypes, whereas the yellows correspond more to the dark phototypes and Asian skins.

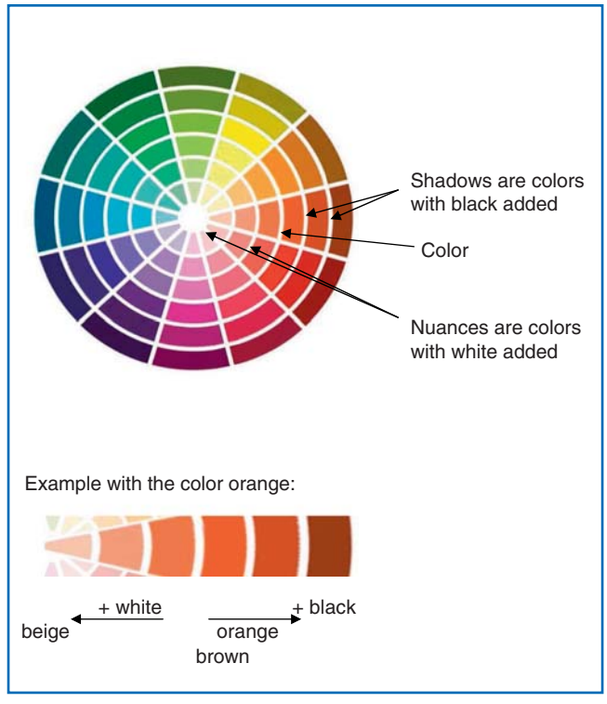

Figure 4. Color values.

For black skins, the concentration in titanium is reduced so that the complexion is not greyed [7].

To avoid a demarcation between the face and the neck, the foundation color should be tested. For the face, the color should be tested on the lower jaw, for the body on the edge of the zone to mask.

Foundation texture

Like the makeup base, the choice of a foundation is important for makeup to wear well.

The textures called "rich" or "comfort" are enriched in emollient agents. Very smooth, they are easy to apply, and even adapted to post-procedure skins.

On the other hand, this type of texture is not optimal on oily skins, for which it is better to choose an oil-free texture that is much richer in powder. It will be less mattifying and will "adhere" to the skin despite the presence of sebum [8].

In addition, the oil-free formulas that have a "second skin" effect are highly appreciated by men because they leave no shininess on the face and they are therefore less visible.

Powder

Powder is indispensable to set the makeup and obtain long wear.

Its mattifying power is also interesting on seborrheic skin.

Since an excess of powder can highlight the visibility of the foundation, it is useful to apply it from the outside of the face toward the center [9]. The result is much more natural, an important point in medical makeup.

In cases of atopic dermatitis, powder is not recommended because it increases the risk of dry skin.

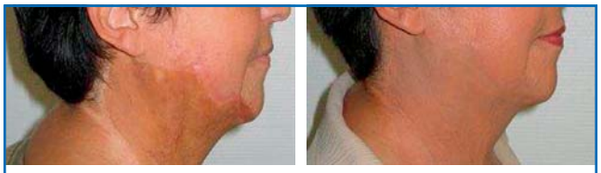

Figure 5. Correction with foundation only.

Powder colors

- The translucent colors set the makeup on light skins.
- The pinks improve dull, olive-colored skins.
- The browns set the makeup of brown to black skins and give a "tanned" appearance to light complexions.

Specificities for makeup of hyperpigmentations

Hyperpigmented lesions are relatively difficult to correct.

The contours are irregular, and foundation alone is not sufficient and also gives a grey aspect to the imperfections.

The makeup base

It is recommended to associate a hydrating sunscreen. However, the superposition of these two products, then a foundation, can leave the skin with a sticky sensation. In this case, it is preferable to replace the moisturizing cream with a moisturizing serum. The skin is softened without a layered effect.

Tone correction

Two parameters should be taken into account: sun protection and foundation.

The indices present in the makeup generally vary from 10 to 30.

The SPF 30 skin tone correction makeup is very useful, particularly since the corrective power is higher.

Coral corrector

Usually women attempt to mask hyperpigmented areas with a foundation or a concealer. The result is rarely satisfactory because the titanium, used to unify and cover imperfections, gives spots a dull and grey color.

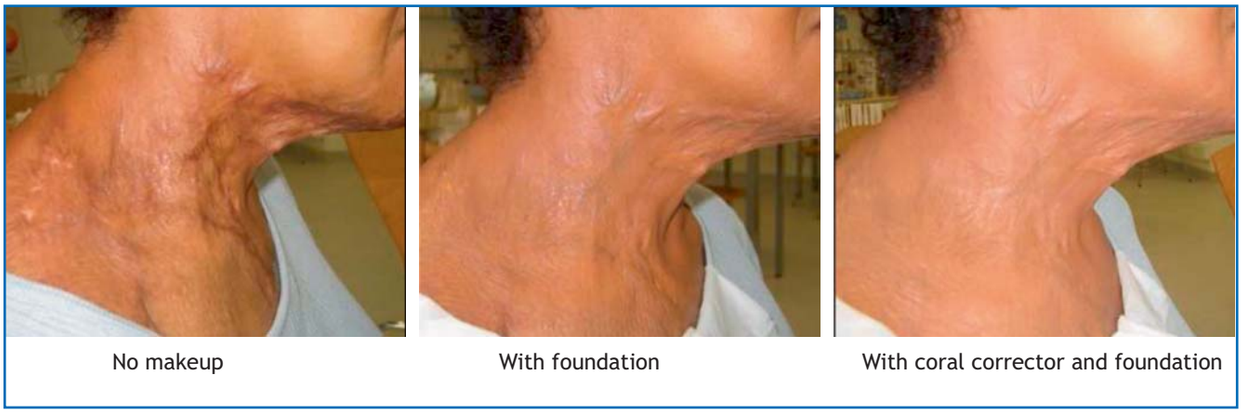

Figure 6. Addition of orange corrector.

On the other hand, if a coral corrector is applied, brown changes to an orange-beige, with no grey reflection, which is very easy to hide with a little foundation (Fig. 7).

In the majority of cases, after application of a coral corrector, the superposition of a foundation unifies the complexion more effectively (Figs. 8 and 9). However, in case of light hyperpigmentation, the coral corrector alone can be sufficient; a little powder can then be used to set it.

The choice of corrector is important in terms of effectiveness as well as its protection index: SPF 30 is currently the highest sun protection index for this type of product.

Compact foundations

The superposition of a compact SPF 30 foundation improves the correction, makes the complexion uniform, and reinforces sun protection.

"Small" brown imperfections (acne scars, lentigines, etc.) require another correction method. In general, it is easier to apply a little bit of compact foundation and then to correct persistent spots locally with a small brush.

The choice of the foundation color is also important to achieve a better result. A yellowship compact foundation with a tone a little higher than the skin complexion can efficiently camouflage the hyperpigmentation.

Powder

The application of a powder adapted to the skin complexion is strongly recommended to prolong the wear of corrective makeup.

When the complexion is unified, the face loses a bit of relief. It is therefore useful to apply a colored powder to "sculpt" the face.

Usually, the color is applied to the cheekbones. However, chloasma located on the cheekbones can reappear with cheek makeup. It is therefore preferable to apply it to the temple area, from the top of the forehead to the jaw. The face thus has relief without highlighting the brown spots.

Figure 7. Chloasma correction with coral cover stick and compact foundation cream

Outdoor makeup

Compact SPF 30 foundation creams are sufficient for brief daily sun exposure. For longer out door periods or during the summer, it is preferable to replace the foundation by a tinted SPF 50 sunscreen.

SPF 50 tinted compact sunscreens are very useful because their percentage in pigments is high and they thus provide good spot coverage.

They also have the advantage of being easier to remove with a paper tissue than a corrector foundation; thus there is less risk of producing a mask effect after several applications [10].

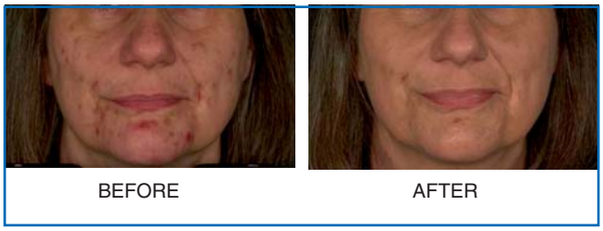

Figure 8. Correction of acne scars.

Conclusion

Medical makeup is adapted to cover up many different skin imperfections while respecting the medical requirements. It is particularly interesting in the case of hyperpigmentation since it combines skin tone correction with sun protection, thus improving the quality of life of patients.

Conflicts of interest statement

J. Nonni: Employee of Avène Dermatological Laboratories

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Figure 9. Correction of lentigos.

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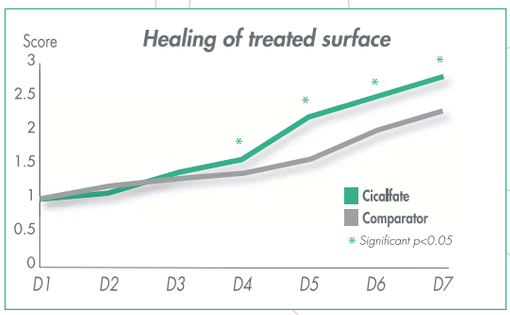

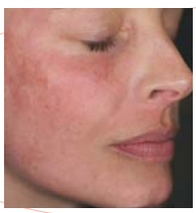
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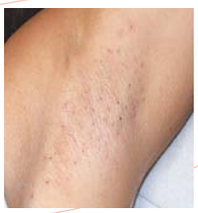
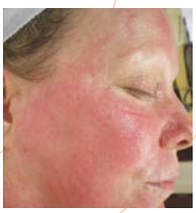

Post-depilatory laser


Post-peel

(1) Monocenter study on suction blisters with 30 subjects – Application of Cicalfate POST-PROCEDURE and a comparator product for 7 days.
(2) Open monocenter study for post-laser treatment and post-peel with 50 subjects – Cicalfate POST-PROCEDURE applied immediately following the procedure and twice daily for 7 days.

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Significant improvement after 1 month, highly significant improvement at 3 months on lentigo [2].

(1) Tolerance and efficacy study on melasma – 82 subjects with phototypes III to VI – product applied once every evening for 3 months- Dermatologist's opinion (DPGA and MASI scores).
(2) Clinical efficacy study on lentigo – 58 subjects presenting at least 5 moderate to severe lesions on the back of both hands, - product was applied once every evening for 3 months – Chromametric measurements (ITA method –D-Pigment RICH) and dermatologist's opinion (DPGA score).

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