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Melasma

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Melasma

Melasma is a common persistent acquired pigmentation disorder of the skin. The term is derived from the Greek word "melas" meaning black. It appears as blotchy, irregular patterned, brown or sometimes grey brown macules on the face and occasionally the neck.

Melasma is commonly found in a rather young age darker skinned individuals, who live in places with increased solar radiation, especially women of Hispanic, Oriental and Indo-Chinese origin.

Many factors have been implicated for the etiology of melasma, but the exact cause of this hypermelanosis is poorly understood. However, it is considered to result from solar radiation and genetic predisposition. Moreover, pregnancy, oral contraception and hormone replacement therapy with natural and synthetic oestrogens, have been involved in the pathogenesis of this hypemelanosis. Despite the fact that melanocytes contain oestrogen receptors that stimulate these cells to become hyperactive, the exact mechanism of estrogens in triggering melasma is unknown [1].

Uncontrolled sun exposure inevitably worsens melasma, while it has been seen to dissolve during periods of sun avoidance.

Recent studies have reported that the three most important etiological factors already mentioned (sunlight, genetic predisposition and hormones) might influence onset or exacerbation of melasma and the combination of these factors often activates the disease [2].

Usually, there is a number of one single or multiple hyperpigmented patches symmetrically arranged, (Figure 1), mainly found on the face and on the cheeks, dorsum of the nose, upper lip (moustache-like melasma) and chin and rarely seen on the V-neck area and upper limbs. Mucosae membranes are not involved. Depending on the location three clinical patterns of melasma are identified: The centrofacial, the malar and the mandibular pattern. Histologically melasma can be classified into three types: epidermal, dermal and mixed. It has been proposed the usage of Wood's light for melasma detection. Nevertheless, recent reports suggested a poorcorrelation between the classifications based on Wood's light and biopsy samples [3]. A more accurate technique like the Reflectance Confocal Microscopy (RCM) provides more precise information on the location and extent of pigment deposit in melisma [4].

Determination of the Melasma Area and Severity Index (MASI) performs subjective evaluations of melasma. MASI is a useful tool in standardizing melasma by dividing the face into four areas: the forehead, the right and left malar area and the chin.

The diagnosis of melasma is clinical. An integral part is the medical history of the patient with all the important information (pregnancy, usage of oral contraceptives, genetic and racial involvement and exposure to sunlight). The Wood's lamp and preferably RCM both assist in the classification of the three above mentioned histological types.

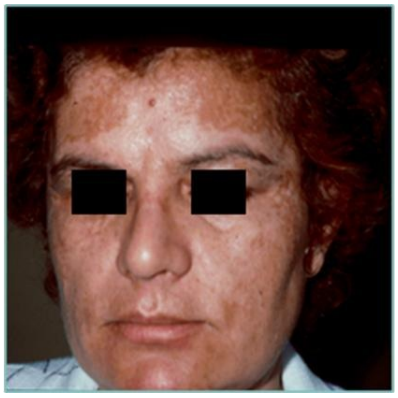

Figure 1: Hyperpigmented patches in Melasma

Treatment

Melasma usually due to its cosmetic issue may cause a negative impact and emotional suffering on the patient. No efficient agent for its treatment is available at present. Most of them can only temporarily de-pigment melasma, with a tendency of recurrence. It is important, before any treatment modality, to consider the factors associated with this hypermelanosis. Nevertheless, numerous therapeutic procedures may offer a significant play an important role.

General therapeutic guidelines

Avoidance of solar exposure. Melanocytes in melasma are easily stimulated by UVB but also by UVA and visible radiation. Consequently, broad spectrum sunscreens should be used daily during and after treatment, throughout the sunny months of the year. An absolute contraindication is sunbathing, because of the possible recurrence of this disorder. Regular use of sunscreens is mandatory for prevention as well as in enhancing the efficacy of other therapies [5].

Women during pregnancy may develop melasma and the everyday usage of broad-spectrum sunscreen is also indicated. The melasma however may dissolve within a few months after delivery.

Women prone to melasma development should not receive any hormonal replacement therapy. Moreover, patients taking contraceptive pills should discontinue them.

Bleaching agents

Classification of the bleaching agents for the treatment of melasma is presented in Table 1.

Phenolic Compounds	Non-phenolic Compounds	Combinations Formulas
Hydroquinone	Azelaic acid	Kligman's Formula
4-isopropylcatechol-4-hydroxyanisol	Retinoids L-ascorbic acid	Kligman's Formula Modifications
Kojic acid	Thioctic Acid	Triple cream
	N-acetylcystein	Other formulas
N-acetyl-glycosamine	Soy Licorice	
4-methoxyphenol	Corticosteroids 4-n-butylresorcinol	
N-acetyl-4-S-cystaminylphenol	Niacinamide Arbutin	

Table 1: Classification of Bleaching Agents

Hydroquinone (HQ)

HQ appears to be the most efficacious bleaching agent. Its action is based on:

a. Retarding melanin biosynthesis by inhibiting the conversion of tyrosine to melanin.

b. Inhibiting the formation or increasing the degradation of melanosomes or both.

c. Inhibiting the DNA and RNA synthesis of melanocytes.

Its efficacy is directly related to the concentration of the preparation, the vehicle used and the chemical stability of the final product. Concentrations of the HQ vary from 2% to as high as 8%. Minimal side effects can be observed when there is a controlled usage of them.

The vehicle is either a hydro-alcoholic solution, with equal parts of propylene glycol and absolute ethanol, or a hydrophilic ointment or a gel containing 0.1% α-hydroxy acids (AHA).

HQ is easily oxidized and loses its potency. In order to maintain the stability of the formulations antioxidants should be used, such as 0.1% sodium bisulfate or 0.1% ascorbic acid. Taking into consideration the desired HQ concentration, the vehicle and the chemical stability the following formula can be prescribed:

HQ 2%-8%

in ethanol and propylene glycol 1:1 (or in a cream base or a AHA 10% gel) Ascorbic acid 0.1% (as preservative)

The side effects are dose-related and are associated with duration and concentration of the HQ. They include allergic contact or irritant dermatitis, (mostly with higher concentrations), guttate hypomelanosis and nail discoloration. They are usually temporary and resolve on HQ discontinuation. Ochronosis is a rare side effect due to the prolonged usage of HQ and is more often seen in black-skin individuals. Ochronosis is defined as a permanent grey-brown or blue-black hyperpigmentation with spotted pinpoint, dark brown (caviar-like) papules (Figure 2) [6].

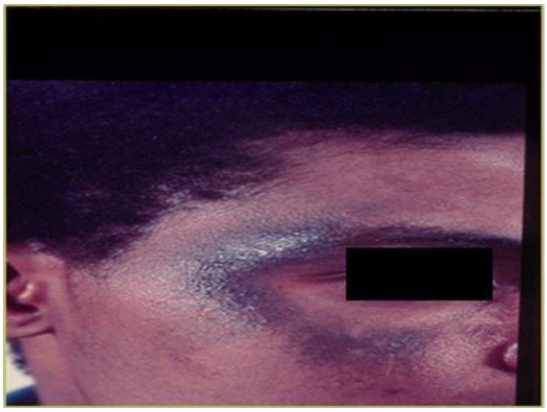

Figure 2: Ochronosis

In the European Union, HQ has been banned from use as a cosmetic ingredient since 2001 for concerns such as ochronosis and occupational vitiligo. However, it is still available as prescription medication; moreover, despite controversies, a review of the literature indicates that HQ is an effective and safe agent for the treatment of melasma, accepted by the FDA in the USA [6].

There is a number of other agents (Table 1) used in topical preparation for the treatment of melasma. The most commonly used agents are summarized as follows:

Azelaic acid: a dicarboxyl acid derived from Pityrosporum ovale (Malassezia ovalis). It may represent a useful second-line topical therapy in patients who cannot tolerate or have access to preparations containing hydroquinone.

Ascorbic acid: may also be a useful adjunctive topical therapy.

Kojic acid: is a fungal metabolic product (Aspergillus penicillium). It may give modest improvement for melasma by inhibiting tyrosinase activity. However, it often causes irritation.

Arbutin/deoxyarbutin and licorice extract: additional studies are needed to determine the role of it in the treatment of melasma.

Combination of HQ and other agents

Combination of HQ with various topical agents as retinoinds and corticosteroids seems to increase efficacy and minimize side effects. The following combination has been proposed: [7]

Kligman and Willis Formula

Hydroquinone 5%

Tretinoin 0.1%

Dexamethasone 0.1%

in ethanol and propylene glycol 1:1 or in hyrdophylic ointment

Tretinoin (retinoid acid), the most commonly used topical retinoid for the treatment of melasma, acts by stimulating cell turnover and thus promoting the rapid loss of pigment via epidermopoieses. Moreover, it acts as a mild irritant, enhances the epidermal

penetration of HQ and prevents the oxidation of HQ. Corticosteroids have several properties. They may inhibit the melanin synthesis through depression of the metabolic activity of the cell and eliminate the irritation caused by HQ and/or tretinoin. This formula is used twice daily for not more than 5-7 weeks, although depigmentation has already begun within 3 weeks. It cannot be preserved by antioxidants and therefore should never be applied after 30 days' time.

A modification of the Kligman and Willis Formula is the following:

Hydroquinone 4%

Tretinoin 0.05%

Hydrocortisone acetate 1%

in ethanol and propylene glycol 1:1 or in hydrophylic ointment

In this formula the concentration of tretinoin is 0.05% and hydrocortisone acetate 1% is used instead of Dexamethasone. The aim is to eliminate the irritation caused by tretinoin as well as the possible side effects, by lowering the concentration of tretinoin and the use of a non-fluorinated steroid.

Both formulations should be kept in a refrigerator at 2-4˚C [8].

One of the most recent and successful combination formulations has been:

hydroquinone 4%

tretinoin 0.05%

fluocinolone acetonide 0.01%

Topical therapy with this triple combination agent seems to be the most clinically effective therapy for patients with melasma [9]. Retinoids as monotherapy are not as effective as the above agents and require more time before any result is visible [10].

Chemical peels for melasma

Glycolic acid 50%-70% peels (every 2-3 weeks) Light Jessner's peels (every 2-3 weeks) Tretinoin 1% (every week) Tretinoin 10% peeling mask Salicylic acid 20%-30% peels (every 2-3 weeks) Pyruvic Acid 50%	4-6 Sessions
TCA 25%-35% peel Jessner's solution plus	Once
After the peel, a maintenance therapy with HQ2% is recommended	

Table 2: Different chemical peels of various concentrations

Chemical peels act by removing excess melanin. Superficial and medium depth chemical peels may be used as a treatment option for melasma in fair skinned individuals. Different chemical peels of various concentrations are summarized in Table 2 and have been used alone or in combination with other depigmenting agents. However, the response of melasma is unpredictable and there is a tendency for pigmentation alterations resulting in a postinflammatory hyperpigmentation, especially in dark skinned individuals.

Several clinical studies showed no additional benefit of Tretinoin and Jessner solution peels than glycolic acid, although less irritation may be caused by tretinoin. Pre- and post-peel regimens are essential factors in conjunction with concomitant topical therapies and photoprotection. In a Jessner solution trial of five patients, stability of the results in their 6-month follow-up visit was obtained only in those patients who continued topical therapy, while the rest showed relapse of the disease [11].

Laser and light treatments

Melanin due to its broad-spectrum absorption permits numerous types of lasers and light sources to be used for the treatment of melasma. Moreover, melanosomes have a short thermal relaxation time. The following types of lasers and light therapies have been proposed in the treatment of melasma:

Erbium YAG

Q-switched

Pulsed CO_2 and Q-switched Alexandrite

Fractional photothermolysis

Intense pulsed light (IPL)

Pulse dye laser (PDL)

Copper bromide laser (very new–under investigation)

It should be highlighted that lasers and light sources may cause damage to the surrounding tissues and subsequent inflammation resulting in a long-lasting postinflammatory hyperpigmentation with a delayed onset. Hence, the above mentioned modalities should be used with extreme caution in Fitzpatrick types IV to VI and when all other methods have failed [6,12-14]. Furthermore, due to the cost and the need for multiple treatments this type of therapy should be considered as a third-line treatment in non-responded to topical preparations or chemical peels patients.

Key points

Q-switched ruby lasers and erbium: yttrium-aluminum-garnet lasers have been shown to worsen melasma.

The combination of carbon dioxide laser with Q-switched Alexandrite laser does not appear to be beneficial for melasma and carried a significant risk of worsening hyperpigmentation in darker-skinned patients.

Fractional resurfacing is approved by the FDA for the treatment of melasma and has been shown to have some benefit; however, additional controlled trials are needed to evaluate its efficacy for melasma.

Intense pulsed light therapy may provide modest benefit as an adjunctive therapy for refractory patients.

Copper bromide lasers may be of benefit for melasma, especially in patients with a visible vascular component, but require further study.

In summarizing all the above data for the treatment of melasma, the following recommendations are suggested for patients with Fitzpatrick's skin types I, II and possibly III and for patients for skin types IV, V and VI (Tables 3 and 4).

First line	Hydroquinone 4% Tretinoin 0,05% Fluocinolone Acet 0,01%	Once at bedtime
For 8 Weeks		
Second line: Chemical peeling or non-ablative fractional photothermolysis		
Maintenance: HQ 2% Cr.-twice daily		
For an indefinite period: Broad Spectrum Sunscreen during sun exposure		

Table 3: Treatment of melasma (Skin Types I-II-(III?))

First line	Hydroquinone 4% Tretinoin 0,05% Fluocinolone Acet 0,01%	Once at bedtime
For 8-10 Weeks		
Second line: Chemical peeling or non ablative fractional photothermolysis		
Maintenance: HQ 2% Cr.-twice daily		
For an indefinite period: Broad Spectrum Sunscreen during sun exposure		

Table 4: Treatment of melasma (Skin Types III-IV-V)

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