Management of Melasma: An Updated Overview

Najla Abubakr Taher *, Manal Mohamed El-Sayed, Hagar Awad Bessar
Dermatology, Venereology and Andrology Department, Faculty of Medicine, Zagazig University, Egypt

Corresponding author: Najla Abubakr Taher
Email: Najlaabubakr1985@gmail.com

Abstract

Background: Melasma is an acquired hyperpigmentation that usually occurs in women. This disorder is characterized by symmetrical and irregular patches on the sun-exposed areas of the face such as upper lips, cheeks, forehead, and chin. Melasma is commonly seen in 39.5% of women in the age range of 22–55 years and 50–70% of pregnant women. Also, its prevalence in men is 5–10.

The treatment of melasma often necessitates a multifaceted approach combining broad-spectrum photoprotection, topical agents, and, in refractory cases, chemical peels and laser/light therapy. Superficial chemical peels, including glycolic, salicylic, and trichloroacetic acid. Lasers and light-based devices, including fractional resurfacing and Q-switched lasers, are also effective in the treatment of refractory melasma, particularly when used in combination with topical depigmenting agents. Microneedling and picosecond lasers have more recently been added to the treatment armamentarium.

Keywords: Melasma, Microneedling.

Introduction:

Face melasma is an acquired pigmentedary disorder that affects many people. This illness is more common in women and those with darker skin, and it is thought to be caused by exposure to ultraviolet light and hormone changes. Melasma is usually a clinical diagnostic consisting of symmetric reticulated hypermelanosis in three primary face patterns: Centrofacial, malar, and mandibular. Women with Fitzpatrick skin types III–V are more likely to develop the condition (1).

Epidemiology:

Melasma is predicted to affect 1 percent of the general population and 9–50 percent of people in higher-risk groups. As a result of the diversity in ethnic backgrounds and amounts of ultraviolet exposure in different geographical places these large ranges are secondary. As a result, no one knows how common it really is. The average age of onset is between 20 and 30 years old. Mandibular melasma patients tend to be in their 40s when it first appears (2).

Frequency rises during pregnancy, as demonstrated in a cross-sectional study in Tehran, where pregnant women had a prevalence of 15.8%. As an example, there was a 50.8% prevalence found in an Indian sample of 2000 pregnant women (2).
Classification of melasma:
The centrofacial pattern affects the forehead, nose, and upper lip, but not the philtrum, cheeks, or chin, in 50–80 percent of instances. Males are more likely to develop mandibular melasma than females, however both patterns are prevalent in women. The latter is more common in the elderly and is thought to be linked to significant photodamage (3).

Extra-facial melasma, a novel type of melasma that can affect non-facial body areas such the neck, sternum, forearms, and upper extremities, occurs less frequently. Because of our inadequate knowledge of the pathophysiology, chronicity, and incidence of recurrence, treating this condition remains difficult despite its prevalence (1).

In the past, melasma has been divided into three types based on their histologic characteristics: epidermal, dermal, and mixed. The latter has both epidermal and dermal subtype histology together. (4).

Histopathology:
The epidermal type has more pigment in the basal and suprabasilar layers of the epidermis than the dermal type. On the epidermis, the melanocytes are often bigger, have prominent dendrites, and produce more melanosomes than normal. With a Wood's light, epidermal pigmentation can be enhanced, making it easier to tell apart epidermal from dermal tissue (5).

Melanophages are found in the superficial and deep dermis of people with the dermal subtype of melanoma. In areas of enhanced melanin deposition, a lymphohistiocytic infiltration may also be observed in the dermis. Solar elastosis and an increase in blood vessels are two other possible observations on the skin. Epidermal and dermal subtypes of mixed melasma coexist in this condition. (4).

Upon histological analysis, melanomas show conspicuous dendritic processes, an increase in epidermal melanin content, a modest rise in the number of dermal melanophages, and minor perivascular lymphohistiocytic infiltration (all present in varying degrees). While melanocytes do not multiply, they do expand and become dendritic, pointing to an elevated metabolic rate. An increase in the amount of melanin in the skin's epidermis and dermis illustrates this. (6).

There is significantly more melanin in all epidermal layers in fontana Masson melasma-stained sections, and in the dermis, there is more free melanin and melanophages than in perilesional skin. Furthermore, pigment basal cells frequently protrude into the dermis in lesional skin. Melasma skin slices stained with periodic acid-Schiff and immunobiologically with anti-collagen IV antibody indicated damage to the basal membrane (7).
Etiopathogenesis:
The etiology of melasma is multifactorial.

- **Melanogenesis and Its Regulation**
  Tyrosinase, TRP1, and TRP2 create melanin in melanosomes. Microphthalmia-associated transcription factor regulates enzyme synthesis (MITF) (8).
  Tyroine kinase receptor Tkr, stem cell factor SCF, melanocortin-1 receptor MITF, and melanocortin-1 ligands promote melanogenesis (MC1R). When MC1R is activated, a transition from pheomelanin to eumelanin synthesis is induced. The SCF-KIT receptor tyrosine kinase pathway promotes MITF and controls melanin formation by increasing tyrosinase activity in the skin (9).

- **Hyperactive Melanocytes**
  TRP1, TRP2, and MITF are all overexpressed in melasma lesions, as are melanocyte dendrites, mitochondria, and golgi bodies as well as the rough endoplasmic reticulum in the lesions. According to these findings, the hyperpigmentation in melasma is not caused by an increase in the number of cells, but rather by an increase in biological activity(10).

- **Role of Inflammation and Reactive Oxygen Species**
  Several environmental conditions, including UV radiation, can cause reactive oxygen species (ROS). ROS interact with cellular lipids, proteins, DNA, and carbohydrates to induce oxidative skin damage. Excess ROS can activate tyrosinase and promote melanin formation, and melasma is linked to an imbalance between the oxidant and antioxidative systems. Melanocyte proliferation, melanin synthesis, and melanosome transfer can all be aided by various interleukins and cytokines. Antioxidant and anti-inflammatory medicines are therefore being researched for their therapeutic potential in melasma(11).
- **Melanosomal Transfer: Protease-Activated Receptor 2**
  Epidermal melanocytes transfer their melanosomes to nearby keratinocytes as part of the melanin-epidermal unit. Melanosomal transfer is inhibited by drugs that block the keratinocyte protease-activated receptor 2 (PAR-2). These drugs have been beneficial in treating melasma. (12).

- **The Defective Skin Barrier in Melasma**
  Impaired stratum corneum integrity has been found in melasma. A ultraviolet radiation-induced, as well well as a de novo downregulation of numerous lipid metabolism genes (such as peroxisome proliferator-activated receptor alpha) resulting in poor generation of free fatty acids leading to a disturbed epidermal barrier (5).

- **The Vascular Component**
  A rise in the production of proangiogenic substances, such as vascular endothelial growth factor (VEGF), leads to the expansion of cutaneous blood vessels. VEGF has the potential to boost melanin formation via binding to VEGF receptors on melanocytes (13).

- **Role of Histamine and the Mast Cells**
  An increased number of mast cells have been detected in the lesional skin in melasma. Ultraviolet radiation causes histamine production and this in turn increases proliferation of melanocytes through the H2 receptors. Ultraviolet radiation also promotes mast cell tryptase activation leading to extracellular matrix breakdown and basement membrane rupture. Mast cells can produce VEGF, transforming growth factor-beta (TGF-β), and fibroblast growth factor-2 all of which increase vascular proliferation therefore contributing considerably to melasma. Despite the prominent significance of mast cells and histamine in the pathogenesis of melasma, antihistamines have failed to offer a meaningful effect in the management of melasma (11).

- **Role of the Estrogen Receptor**
  Melasma is typically encountered among women in the reproductive age group notably during pregnancy or with oral contraceptive use (14). Estrogens upregulate the synthesis of enzymes involved in melanin production such as tyrosinase, TRP-1, TRP-2, and MITF, and also upregulate estrogen receptors in the lesional skin (13).

**Diagnosis:**

**Clinical manifestations:**
Typically, melasma manifests as asymptomatic, symmetrically distributed, well-demarcated macules/patches with serrated, irregular, and geographic borders. The macules/patches normally form gradually over time. Pigmentation might be guttate, confetti-like, linear, or confluent. The colour varies from light brown to dark brown to bluish grey (15).

**Clinical assessment:**
Epidermal melasma is usually light brown, and Wood light enhances the color contrast between hyperpigmented areas and normal skin. Dermal melasma tends to be bluish or grayish due to the Tyndall effect and exhibits no accentuation of color contrast under Wood light. The mixed type is usually dark brown with variable enhancement on Wood light examination. Using a Wood’s lamp,
the hyperpigmentation can be accentuated when the pigment is epidermal (16).

Dermoscopy is employed in the diagnosis of melasma because it allows the physician to see the vascular component, which is present in a substantial proportion of the population. Distant reticular pigmentation in varying hues of brown can be seen in the lesions of melasma, with the follicular openings being sparse. The density and location of melanin can be determined by the colour intensity of melanin and the regularity of the pigment network in the skin. When it is found in the stratum corneum, it has a dark brown colour and a well-defined network; when it is found in the lower layers of the epidermis, it has shades of light brown and irregularity in the network; and when it is found in the dermis, it has a blue or bluish-gray colour and a well-defined network. (17). Melasma has also been studied at the cellular level using reflectance confocal microscopy (RCM). On histology, it showed an increase in hyperrefractile cobblestone cells in the epidermis, which corresponded to hyperpigmented basal keratinocytes. (18).

![Figure 2](Image)

**Figure (2):** Dermoscopy of epidermal type of melasma shows vasculature and brownish regular pigmented network (17).

![Figure 3](Image)

**Figure (3):** Different patterns of melasma (19)
Measuring the severity of melasma can be difficult because of the wide range of presentation. For the evaluation of clinical appearance and psychosocial impact of melasma-related dyspigmentation, several validated methods have been developed. For this reason, standard instruments are now better suited to evaluating the therapeutic effectiveness of various melanomas in clinical trials (20).

To gauge the severity of face hyperpigmentation, dermatologists utilise the Melasma Area and Severity Index (MASI). Area-weighted scores of pigmentation and homogeneity on the forehead, chin, and right and left malar cheeks are used to produce this number. The modified MASI (mMASI) was produced when homogeneity was removed from the computation because of the decreased inter-rater reliability of that statistic. A global score that encompasses empirical data as well as the subjective assessment of the patient has been developed by correlating it to the Melasma Severity Score (MSS). (20).

For many dermatologic conditions, a health-related quality of life (HRQoL) tool has been used to measure the psychosocial aspects of skin diseases. The most commonly used tool that reliably measures the effect of melasma on quality of life is the MelasQol. The MelasQol is a questionnaire containing 10 questions regarding the impact of melasma on the emotional condition, social relationships, and daily activities of patients. The patient ranks on a scale of 1 (not bothered at all) to 7 (bothered all the time) how he or she feels about the melasma. The total score is calculated by the sum of all scales for each question (total score ranges from 10 to 70) (15).

**Treatment:**
Topical, oral, procedural, and combination therapies are available for melasma. Photodamage, inflammation, vascularity and pigmentation are only some of the pathogenesis-targeting elements of these drugs (21).

**Table (1):** Melasma treatments, mechanisms of action, and adverse effects (21)
General considerations
Because of its chronic and recurring nature, treating melasma can be difficult. In the course of and following therapy, patients should be educated on the need of using broad-spectrum sunscreens and avoiding the sun whenever possible. Skin-lightening chemicals, chemical peels, and laser and light therapy are all options for treatment. Patients with persistent cases of melasma generally receive a mix of agents or treatments because no one therapy has been shown to be useful for all of them. (22).

Photoprotection
Whichever technique is used to treat melanomas, it's essential to pair it with sun protection measures like avoiding the sun, wearing a wide-brimmed hat, and applying broad-spectrum sunscreens that block both UVA and UVB rays simultaneously. Patients with any type of melasma should wear a daily broad-spectrum sunscreen with an SPF of 30 or higher, according to most studies. A sufficient amount of sunscreen should be applied prior to venturing out, and it should be reapplied every two hours while you're out in the sun. Preventing pregnancy-related melasma may be as simple as using broad-spectrum sunscreens on a regular basis (23). Types of sunscreens adapted from

First-line therapies
Skin-lightening agents
Topical skin-lightening agents are the mainstay of treatment of melasma. Most target tyrosinase, which converts L-tyrosine to L-3, 4-dihydroxyphenylalanine (L-DOPA) and is the rate-limiting enzyme in the melanin synthesis pathway. Skin-lightening agents commonly used in the treatment of melasma include:
● Hydroquinone
In nature, hydroquinone is a hydroxyphenolic molecule that prevents tyrosinase from doing its job. Topical hydroquinone preparations have hydroquinone concentrations ranging from 2 to 4%. Hydroquinone's side effects include erythema, stinging, and desquamation. The highest concentration is the most effective, but it may also cause more severe irritating contact dermatitis, hypopigmentation of the surrounding skin, and even exogenous ochronosis. (24).

- **Azelaic acid**
  Azelaic acid, a naturally occurring, nonphenolic, nine-carbon dicarboxylic acid, inhibits tyrosinase by posing a competitive threat. Hydroquinone 2 percent and hydroquinone 4 percent were found to be more effective with azelaic acid 20% cream or 15% gel in randomised trials. Azelaic acid side effects include erythema, burning, scaling, and itching (25).

- **Mequinol**
  MEQONOL (hydroquinone monomethyl ether) is an anti-tyrosinase drug that competes with 4-hydroxyanisole (4-hydroxyanisole). Tretinoin and mequinol have only ever been tested together for the treatment of sun spots, and side effects of mequinol include sun spots, sunburn, and desquamation (26).

- **Kojic acid**
  Tyrosine is converted to melanin by chelating copper at the active site of the enzyme known as tyrosinase, which is found in the skin. It is possible that kojic acid, in addition to irritating the skin locally, could also induce allergic contact dermatitis (27).

**Topical retinoids**
To accelerate keratinocyte turnover, reduce melanosome transfer, and allow other active substances to penetrate better, tretinoin (all-trans retinoic acid) works as an antioxidant. Topical retinoids, which are recognized teratogens, should not be taken or continued during pregnancy. Topical retinoids have not been linked to an increased risk of birth defects, however. (28).

**Combination formulations**
Combinations of topical agents (eg, hydroquinone, tretinoin, azelaic acid) include dual and triple combination of skin-lightening agents (29).

- A triple combination formulation of tretinoin 0.05%, hydroquinone 4%, and a mid-potency topical steroid, fluocinolone acetonide 0.01% (Tri-Luma), appears to have greater efficacy in treating facial melasma than hydroquinone alone or combinations of two of the components (30).
- A combination of mequinol-tretinoin (Solage) was found to be as effective as 3% hydroquinone in reducing the pigmentation of facial lentigines, however, complete clearing of lesions was uncommon with either treatment. The efficacy of mequinol/tretinoin in the treatment of melasma has not been established (26).
- Hydroquinone 4% in combination with 10% glycolic acid, antioxidants, and sunscreens (Glyquin) appears to be effective in decreasing the degree of pigmentation in patients with melasma. Irritation was a frequent side effect but resolved with the application of moisturizers and temporary cessation of treatment. Many other hydroquinone-based formulations are commercially available. They may contain a variety of agents, such as glycolic acid, antioxidants, broad spectrum sunscreens, retinol, and moisturizers (31).

**Second-line therapies**
Chemical peels

Chemical peels may be indicated for patients with moderate to severe melasma that has not responded to skin-lightening agents. A chemical peel is a procedure in which a topically applied wounding agent creates smooth, rejuvenated skin by way of an organized repair process and exfoliation. There are three types of chemical peels: superficial, medium-depth, and deep. Superficial peels such as glycolic acid peel and salicylic acid have shown safety and efficacy with few adverse effects (10). Treatment begins with the application of low concentrations of the peeling agent, followed by gradual titration up on a weekly to monthly basis, depending upon the response and degree of skin irritation. Topical skin-lightening agents are frequently used before and in between peels and appear superior to topical retinoids as priming agents when used in combination with chemical peels. However, the response to chemical peeling varies, and caution must be used to avoid further dyspigmentation (29).

Laser and light sources

Lasers and light-based therapies for the treatment of melasma should be used only in refractory cases and with extreme caution, especially in patients with skin phototypes IV to VI. Several types of lasers have been used for the treatment of melasma with variable results, including the Q-switched neodymium: yttrium-aluminum-garnet (Nd:YAG) laser, Q-switched ruby laser (32), Q-switched alexandrite laser combined carbon-dioxide (CO2) laser (33), Erbium:YAG laser (34), Nonablative 1550-nm and 1927-nm thulium fiber fractional lasers (34), and intense pulsed light (IPL) (35).

Adverse events of laser therapy included erythema, scaling, dryness, stinging or burning, edema, and hypo- or hyperpigmentation. Until more definitive studies are available, the decision whether or not to try laser therapy should be made on a case-by-case basis (36).

Other treatments

Rucinol (4-n-butylresorcinol), a derivative of resorcinol that inhibits the activity of tyrosinase and tyrosinase-related protein-1, has been evaluated for the treatment of melasma. Tranexamic is a plasmin inhibitor and lysine analog that has been shown to inhibit ultraviolet radiation-induced pigmentation in animal models intradermal tranexamic acid injections. Oral tranexamic acid, alone or in combination with topical skin-lightening agents (37).

An oral preparation of procyanidin, a polymer of flavonoids extracted from the maritime pine bark (Pycnogenol), and vitamins A, C, and E has been evaluated with a reduction of pigmentation measured with a skin colorimeter and a decrease in the MASI score (38).

Microneedling

Another adjunctive treatment is microneedling or mesotherapy, which creates small channels in the skin to deliver small amounts of topical drugs intradermally. The skin punctures induced by microneedling can also stimulate a beneficial wound-healing response with fewer side effects compared to conventional resurfacing procedures. This technique may result in a deeper and more even placement of the medication to the epidermis and dermis (9).

In a randomized study using multiple microinjections of TA intradermally compared to cycles of microneedling alone followed by the application of topical TA, Possible clinical benefit was shown with use of microneedling but no statistically significant benefit (39).
Curcumin, lignin, metformin, niacin amide, liquiritin, soy milk, soy bean, liquorice extract, orchid extract and coffeeberry extract (11).

**Monitoring**

Patients on long-term treatment with skin-lightening agents containing topical hydroquinone and corticosteroids should be monitored for the occurrence of exogenous ochronosis or skin atrophy. Exogenous ochronosis is a rare, adverse effect associated with high concentrations and prolonged use of topical hydroquinone. It manifests as a localized, symmetric, blue-gray discoloration of the skin, with characteristic hyperchromic, pinpoint, caviar-like papules in photo-exposed regions (18).

**Maintenance therapy**

Sun avoidance and sun protection are essential to achieve and maintain the results of depigmenting treatments. In addition to photoprotection, intermittent application of single agents (eg, hydroquinone, azelaic acid, and topical retinoids) or triple-combination creams may be helpful in preventing recurrences in patients who achieved complete or almost complete clearance after continuous treatment. During the maintenance phase, topical preparation can be applied once a day to three times per week; continuous treatment can be resumed if a relapse occurs (40).

**Refractory melasma**

Superficial or medium-depth chemical peels alone or in combination with topical agents can be used as a second-line therapy in patients who do not respond to combinations of skin-lightening agents. Agents that have been evaluated for the treatment of melasma include glycolic acid 20 to 70%, salicylic acid 20 to 30%, and TA 15 to 20%. However, studies have provided inconclusive results, and their efficacy remains unproven. Caution must be used in patients with darker skin since dyspigmentation may result from the chemical peel procedure (41).

Laser and light-based therapies are another option for patients with refractory melasma. The risks and the benefits of laser therapy must be carefully considered and individualized based upon the patient’s skin type and previous response to treatment. Extreme caution must be used in patients with darker skin due to the risk of worsening the disease (41).

**Camouflage techniques**

Because melasma typically occurs on the face, this disorder can be emotionally and psychologically devastating to affected patients. Camouflage techniques may be helpful in the management of melasma. Mineral makeup, which contains titanium dioxide and zinc oxide, functions not only as a way to cover up the facial discoloration but also as an effective sun-protection agent. The usual method of application uses simple techniques to apply a fine layer of camouflage cream, followed by a setting powder. Although the products contain sun protection, additional (oil-free) sunscreen can be applied under the camouflage makeup. The patient’s topical medication or emollients can be applied before the camouflage (42).

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