

Management of Melasma: Emerging Facts

Rabin Jung Thapa, Bal Chandra Karki, Satish Chandra Yadav*
Chongqing Medical University, Chongqing, China.

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***Corresponding author:** Satish Chandra Yadav,
Chongqing Medical University, Chongqing, China.

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Abstract

Melasma is a dark or tan discoloration of the skin, whose exact cause is still unclear however sun exposure, hormonal influences, phototoxic drugs, and genetic factors are some of attributing factors. It is more common in females; with an 80% distribution is Centro-facial. Pathophysiologically, melasma shows the surge in dermal and epidermal pigmentation along with melanosomes, perivascular lymphohistiocytic infiltrates, and expansion of melanocytes. The latest treatment regimens include oral, topical, and procedural therapies. Conventional treatment of melasma includes hydroquinone, tretinoin, corticosteroids, and triple combination creams; Tranexamic acid, Polypodium leucotomos, and glutathione are newer drugs that have shown propitious effects. Techniques such as chemical peels, micro-needling, radiofrequency, and laser are also widely used as first-line or complementary treatments for melasma. Combing different treatment modalities have shown better efficacy than monotherapy. The objective of this review is to update the current emerging treatment modalities of melasma.

Keywords: Melasma; pigmentation, triple combination creams, laser

Introduction

Melasma is a word that came from a Greek root, Melas means black. Melasma (also called chloasma faciei (1)) is a dark or tan discoloration of the skin. The exact cause of melasma is still unclear however some attributing factors are sun exposure, hormonal influences, phototoxic drugs, and genetic factors (2). This disorder is more common in female especially pregnant women (also known as the mask of pregnancy) and those taking pills and hormonal therapy (3). Clinically, Melasma is hyper-melanosis generally present in symmetric patterns: The most common pattern is Centro-facial up to 80% of patients have pigmentation on the forehead, nose, and upper lip, excluding the philtrum, cheeks, and chin (4, 5). The malar and mandibular lesions are seen on the cheeks, nose, and ramus of the mandible respectively are less common. Extra-facial melasma is a newer pattern commonly seen on the neck, sternum, forearms, and upper extremities (6). The treatment of melasma is very challenging, due lack of clear pathophysiology. However, the latest regimens that include oral, topical, and procedural therapies are a revolution in the field of melasma treatment.

Epidemiology of Melasma

The exact prevalence of melasma is still unknown, due to variation among geographic locations and ethnic groups. However, most studies reported that the prevalence of melasma varies from 1 to 50% among the general population to high-risk populations (7-10). The most common age of onset is 20-30 years (5, 11), but mandibular types are seen in the patients in their 40s (12).

Melasma is most common in women than in men in the 9:1 ratio: however, a study from Brazil and India found the ratio 39:1 and 4:1 respectively (13, 11). The prevalence of melasma among pregnant women ranges between 15 and 50 percent (7, 8). The global prevalence of melasma varies in different locations 8.8% in Latino women (9), 2.9% in Saudi women (14), and 1.5% in Ethiopian women (15). The causes of Melasma are multi-factorial. However, UV light plays an important role in triggering and exacerbating melasma. UV light produces reactive oxygen through nitric oxide



activation resulting in melanogenesis. A recent study found that visible light of 415nm wavelength can cause enlarged pigmentation that could last for 3 months. Pathophysiologically, melasma shows the surge in dermal and epidermal pigmentation along with melanosomes, perivascular lymphohistiocytic infiltrates, and expansion of melanocytes.

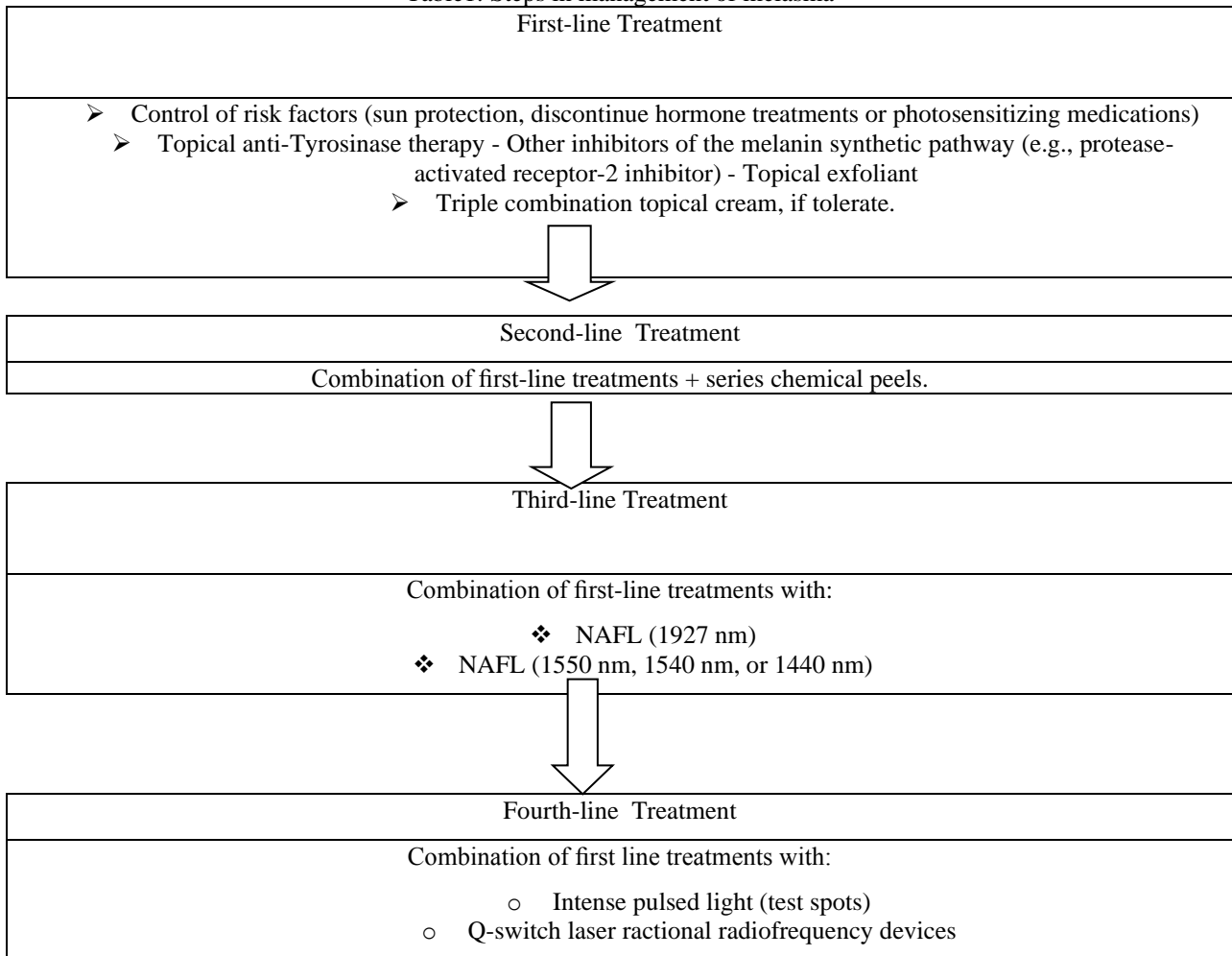
Treatment

The treatment of melasma is arduous, due to inadequate responses and multiple relapses. The best clinical effects are achieved by combining therapy that targets various pathologic aspects, such as photo-damage, inflammation, distorted vascularity, and unusual pigmentation. The combination therapy includes topical, oral, and procedural techniques, which limit melanin synthesis, epidermal

turnover, and remove melanin without influencing its biosynthesis or melanosome transfer from melanocytes to keratinocytes (16-18).

The management of melasma typically starts with the elimination of risk factors, strict ultraviolet sun protection, and topical lightening formulations (such as botanical, corticosteroids, retinoid, and hypo pigmenting agents). These treatments may temporarily improve the skin condition but the pigmentation often returns, therefore the main goal includes the inhibition of pathways that synthesize melanin, a decrease of melanosome transfer from melanocytes to keratinocytes, and acceleration of pathways to remove melanin. The proposed therapeutic ladder for Melasma management is shown in (Table 1).

Table 1: Steps in management of melasma



Source: M.K. Trivedi. Int J Womens Dermatol. 2017 Mar; 3(1): 11–20

Topical Treatment

Topical applications are the first-line treatments for melasma. Targets of topical agents are to disrupt the enzymatic processes of pigments production. In many cases, topical agents are used according to the states of disease but the condition, more often than not, relapses (19). Topical agents are frequently used in combinations with other treatments such as chemical peels, lasers, and intense pulse light sources. Since it is a long-term treatment plan, it is wise to take a detailed history of oral contraceptives or

any phototoxic, anti-seizure medications and the usage of cosmetics. The patient should avoid the use of scented cosmetics and oral pills. Topical agents are exceedingly beneficial in the epidermal type of melasma (20).

A. Hydroquinone (HQ)

Hydroquinone (HQ), also known as dihydroxybenzene is an aromatic organic compound of phenol type; which decreases the formation of melanin in the skin. Melanin is the pigment that gives



brown color to the skin. Hydroxyphenolic compounds are structurally similar to precursors of melanin. Dihyric phenol inhibits the conversion of DOPA to melanin by the tyrosinase enzyme, which results in the prevention of melanin synthesis (21). The formation, melanization, and degradation of melanosomes are affected by hydroquinone (HQ). It further affects the structures of melanocytes which cause necrosis (22).

HQ is chiefly used to treat depigmentation. It has remained the gold standard for the treatment of melasma. For melasma treatment, (2-4)% concentration of HQ preparations are used once daily. Effects are noticeable after 5 to 7 weeks; however, treatment should be continued for three months to one year at least. HQ is often used with other combinations like glycolic acids, topical steroids, retinoids, and sunscreens (20). HQ combines with Kligman's formula, Modifilide Kligman's, Westerhof's formula, and Pathak's formula. Kligman's formula (5% HQ, 0.1% tretinoin and 0.1% dexamethasone). Modified Kligman's (4% HQ, 0.05% tretinoin, and 1% hydrocortisone acetate). Westerhof's formula (4.7% N-acetylcysteine, 2% HQ and 0.1 triamcinolone acetonide) (23).

The adverse reactions of HQ are related to its dose and treatment durations. The major complication is skin irritation while mild burning, redness (erythema) stinging, dryness, allergic contact dermatitis, nail discoloration, transient hypochromia, and paradoxical post-inflammatory hypermelanosis are also seen (23).

B. Azelaic Acid (AZA)

The exact mechanism of action of azelaic acid is unspecified. However, in a vitro study it has been observed that, it inhibits nine carbon dicarboxylic acid of tyrosinase, resulting in antiproliferative and cytotoxic effects (17,24). Studies have also shown that 20% azelaic acid cream is as effective as 4% Hcqs cream but more effective than 2% Hcqs cream alone (25,26). It takes 1-2 months to produce skin lightening effects (20). The adverse effects of Azelaic Acid are Pruritus, tingling, stinging, mild erythema, peeling and burning (27).

C. Kojic Acid (KA)

Kojic acid is a 5-hydroxy-2-hydroxymethyl-4-pyrone, which is a chelating agent and has an anti-oxidant effect. Kojic Acid inhibits tyrosinase by chelating copper at the enzyme's active site. It is derived from fungi namely *Acetobacter*, *Aspergillus*, and *Penicillium*. 2% Kojic acid cream widely used in Asia, however less effective than Hcqs and causes skin Irritation and sensitization (28-31).

D. Tretinoin

Tretinoin is the carboxylic acid form of vitamin A, also known as all-trans retinoic acid (RA). Tretinoin improves pigmentation by inhibiting several steps in the melanization pathway. Retinoids, such as tretinoin, vitamin A and retinoic acid (RA) were first used in combination with HQ. Later penetration introduces its effect on melanogenesis (32, 33). Tretinoin assists in the rapid loss of pigment through epidermopoiesis and increased epidermal turnover also decrease the contact time between keratinocytes and melanocytes. Additionally, there is evidence to inhibit the induction of tyrosinase melanogenesis and DOPA chrome

conversion factors (34). Clinically significant skin lightening becomes evident only after 24 weeks. Tretinoin can also be used as a peeling mask. Tretinoin has a good therapeutic response but better results are obtained in combination with agents like HQ and corticosteroids (35). The most common side effect of tretinoin is erythema, a retinoid dermatitis characterized by burning, stinging, dryness, and scaling. Tretinoin can be irritating must adjust to prevent inflammation. Inflammation can cause hyperpigmentation, predominantly in people with dark skin (33,36). It is better to use sunscreens during treatment with retinoic acid to avoid its side effects.

E. Corticosteroids

Corticosteroids are hormones that are produced in the adrenal cortex of vertebrates, but synthetic analog are also available. Corticosteroids are of two types: One is glucocorticosteroids another one is mineral corticosteroids. Pigmentation can be prevented by non-selective suppression of melanogenesis with anti-inflammatory effects (37). Corticosteroid inhibits the synthesis of melanin, and its mediators like prostaglandin and leukotriene, which result in skin lightening. Therapeutic responses are good, however less effective than other depigmenting agents when used alone (38). Topical steroids can be used solely, however, long-term benefits are fewer and more side effects: rosacea-like dermatosis (erythema, Pustules, and papules on Centro facial area), dermatitis, hypertrichosis, epidermal atrophy, steroid-induced acne, and telangiectasia are seen.

Oral Treatment Of Melasma

Most commonly used oral therapies for Melasma management are Tranexamic Acid (TA), Polypodium Leucotomos and Glutathione.

A. Tranexamic Acid (TA)

The hemostatic agent, Tranexamic acid, is a synthetic derivative of lysine; It inhibits the binding of plasminogen to the receptor expressed by keratinocytes, which results in the reduction of UV-induced plasmin activity, tyrosinase activity, prostaglandin production as well as melanocyte-stimulating hormone levels (39, 28, 40). It also inhibits angiogenesis, a contributing factor of melasma by reducing vascular endothelial growth factor (VEGF) and endothelin-1, chemical signals (28, 41,42). The oral dose of Tranexamic acid is 250mg two times daily as adjunctive therapy in patients who do not have an effective result with Hcqs or triple therapy cream (43). The common side effects of Tranexamic acid are pale skin, headache, tinnitus, abdominal bloating, irregularities of the menstrual cycle, mild gastrointestinal discomfort, allergic skin rashes, alopecia, and deep venous thrombosis (DVT) (44).

B. Polypodium Leucotomos

Polypodium leucotomos is a fern found in south and central America, is currently used as an oral medication for the treatment of melasma (39, 45--47). It inhibits cyclooxygenase-2 triggered by UV radiation and promotes expression of the p53 suppressor gene, modulation of inflammatory cytokines, and upregulation of endogenous antioxidant systems (48). When used with



hydroquinone, *P. leucotomos* extract may expedite clinical improvements. A study carried out in 33 Asian women showed that 12 weeks treatment with topical Hcqs 4%, sunscreen SPF 50+ and oral *P. leucotomos* extract; 75% improvement in MASI scores (49). The recommended dose of *P. leucotomos* extract is 480-1200mg daily, with no major side effects (39).

C. Glutathione (GSH)

Glutathione is an endogenous anti-oxidant that consists of three amino acids namely glutamine, cysteine, and glycine. It prevents cellular damage caused by reactive oxygen; inhibits tyrosinase to reduce inflammation, and produces skin whitening effects due to an increase in pheomelanin ratio compared to eumelanin (28, 50). A study in 2016, showed that 500 mg glutathione lozenge taken once daily for eight weeks has a significant decrease in melanin level (50). A similar study was carried out in 2014, where 2% glutathione lotion was used twice daily for 10 weeks, which showed 67% skin whitening (51). No major side effects were seen with lozenge or lotions.

Chemical Peels

Chemical peels have been frequently used in the treatment of melasma as they can increase epidermal remodeling and keratinocyte turnover. The most commonly used peels are glycolic acid (GA). A study in 2016 found that a combination of 20 percentage Salicylic acid and 10 percentage mandelic acid are as effective as 35 percent glycolic acid over 12 weeks of treatment (52). Another chemical peels Trichloroacetic acid, 10-20 percent of TA has the same effect as GA peels however it has more side effects like burning and peeling (53).

Micro Needling

Microneedling or mesotherapy is a process to distribute a small number of topical drugs intra-dermally by making tiny channels in the skin (54, 55, 56). It also helps in the placement of drugs to the deeper epidermis and dermis; Also stimulates wound healing response (55, 56). A study carried in 2011 showed that delivering topical drugs with micro needling significant improvement of MASI scores (54). The common side effects are Erythema, Tram track marks, and Post-inflammatory Pigment alteration.

Lasers And Light Therapies

LASER stands for light amplification by stimulated emission of radiation are devices that release electromagnetic radiation that can be used to ablate tissues. Recently, a laser has been commonly used for the treatment of melasma. It is based on the principle of selective photothermolysis that selectively targets chromophores cells. The wavelength and duration of light are short, that are easily absorbed by chromophores cells, which result in selective heating and thermal injury to the pigmented tissues (57-59). The various wavelengths of laser penetrate varying depths, which help clinicians to target various depths in melasma.

Nonablative fractional lasers –It has the slowest chance of recurrence after treatment while quality-switched (QS) lasers have a rapid recurrence rate (18). The wavelength of 1927 nm is effective against epidermal pigmentation, and wavelengths of 1440, 1540, and 1550 nm are effective against dermal melasma

(18). **Quality-switched neodymium-doped yttrium aluminum garnet (QS-Nd: YAG)** – The wavelength of 1064 nm is effective against the melasma, as it damages the upper dermal vascular plexus and help in collagen formation (80). Despite the rapid relapse (18), QS-Nd: YAG laser is most commonly used (60).

Pulsed dye laser (PDL) –It is very useful for vascular lesions as angiogenesis contributes to melasma formation (41,42,61,62). **Intense pulsed light (IPL)** –It emits light of 500 to 1200 nm wavelength which helps the clinician to modulate wavelength, the duration for accurate targeting of melasma cells resulting in thermolysis (60). A study conducted in 2010, found that IPL use in hyperpigmented areas and dark tones have excellent results in 47% while 29% good and 13% has moderate results (63). Since IPL targets all layers of skin, it can damage normal skin, thus not recommended for darker tones (Fitzpatrick skin types IV through VI).

A study carried out in 2010, among 22 Asian patients who were treated with 2% hydroquinone alone or a combination of laser with hydroquinone 2%, the result showed that the MASI score and colorimetric relative lightness score improved by 76% and 93% in combined treatment while 24% and 20% improvement in hydroquinone alone side (64). In 2018, A Korean doctor treated 40 patients with a QS-Nd: YAG laser for 10 weeks, study showed a 54% improvement in MASI scores after 10 weeks, 30 patients had better improvement while 4 patients had no improvement post-laser (65). A similar study was carried out by Kauvar AN in 27 patients, who were treated with the combination of microdermabrasion followed immediately by QS-Nd: YAG over 4 weeks. 50% showed improvement within a month, while 95% clearance was seen in 40% of patients over 3 to 12 months. Side effects: Melasma pigmentation may get worse or streaked hypopigmentation may be seen post-laser treatment. It is wise to use sunscreen post-laser.

Melasma treatments, Mechanisms of Action, and Adverse Effects are shown in Table 2. The treatment of melasma is still challenging due to unclear causes and multiple relapses post-treatment. Among the current topical treatment, Hydroquinone is the gold standard. Nowadays hydroquinone, retinoic acid, and corticosteroids are the first-line treatment for this pigmentary disorder. Procedural treatments are famous in this era such as chemical peels, IPL, micro-needling, and laser. Still, we need more research about melasma, for better understanding of the causes and treatment.

**Table 2:** Medicines,MOA and its effects

Modality	Drugs	Mode of action	Side effects
Topical	Hydroquinone (HQ),	<ul style="list-style-type: none"> ✓ Tyrosinase inhibitor. ✓ Melanocytes DNA and RNA synthesis inhibition 	Irritation, exogenous ochronosis (with HQ)
	Azelaic acid,	<ul style="list-style-type: none"> ○ Tyrosinase inhibition ○ Melanocyte proliferation inhibition 	Irritation, erythema, Pruritis
	Kojic acid	<ul style="list-style-type: none"> • Tyrosinase inhibition • ROS scavenger 	Irritation, sensitization
	Tretinoin Corticosteroids	Increased keratinocyte turnover Anti-inflammatory with non-selective inhibition of melanogenesis	Irritation, redness Telangiectasias, epidermal atrophy, steroid-induced acne, striae, hypopigmentation
oral	Tranexamic acid	Inhibits plasminogen/plasmin pathway → inhibition of melanin synthesis Decreases vascular proliferation Inhibition of reactive oxygen species	Abdominal bloating, menstrual irregularities, headache, deep venous thrombosis No significant AE
	<i>a. Polypodium leucotomos</i> b. Glutathione		
Procedural	Q-switch ruby laser, Q-switch Nd:Yag laser	Melanosome destruction	Burn, post inflammatory pigment alteration (PIPA)
	Non-ablative fractional lasers. Chemical peels	Fractional photothermolysis leading to melanin extrusion. Increased keratinocyte turnover	Burn, PIPA Burn, peeling, PIPA
	Microneedlings	Transdermal drug delivery.	Erythema, edema, tram-track marks, PIPA
	Intense pulsed light	Extrusion of melanosomes	Burn, PIPA
	Radiofrequency	Cellular biostimulation Transdermal drug delivery	Burn

Source: Oluwatobi A. Ogbechie-Godec . Nada Elbuluk ; Dermatol Ther (Heidelb) (2017) 7:305–318

List of Abbreviations

AzA	Azelaic Acid
HQ	Hydroquinone
IPL	Intense Pulsed Light
KA	Kojic acid
MASI	Melasma Area and Severity Index
NAFL	Nonablative Fractional Laser
GSH	Glutathione
Nd:YAG	Neodymium-Doped Yttrium Aluminum Garnet
PIH	Post-inflammatory hyperpigmentation
PIPA	Post-Inflammatory Pigment Alteration
QSRL	Q-switched ruby laser
RF	Monopolar radiofrequency

ROS Reactive Oxygen Species

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