Melasma: an Up-to-Date Comprehensive Review

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ABSTRACT

Melasma is a common acquired condition of symmetric hyperpigmentation, typically occurring on the face, with higher prevalence in females and darker skin types. Multiple etiologies, including light exposure, hormonal influences, and family history, have been implicated in the pathogenesis of this disorder. Overall prevalence ranges widely at 1–50%, since values are typically calculated within a specific ethnic population within a geographic region. Histologically, melasma can display increased epidermal and/or dermal pigmentation, enlarged melanocytes, increased melanosomes, solar elastosis, dermal blood vessels, and, occasionally, perivascular lymphohistiocytic infiltrates. Various topical, oral, and procedural therapies have been successfully used to treat melasma. Traditional topical therapies including hydroquinone, tretinoin, corticosteroids, and triple combination creams; however, other synthetic and natural topical compounds have also shown varying efficacies. Promising oral therapies for melasma include tranexamic acid, Polypodium leucotomos, and glutathione. Procedures, including chemical peels, microneedling, radiofrequency, and lasers, are also often used as primary or adjunctive treatments for melasma. Notably, combination therapies within or across treatment modalities generally result in better efficacies than monotherapies. This review serves as a comprehensive update on the current understanding of the epidemiology, pathogenesis, clinical and histologic features of melasma, as well as treatments for this common, yet therapeutically challenging, condition.

Keywords: Hyperpigmentation; Melasma; Pigmentary disorders; Skin of color

INTRODUCTION

Melasma, formerly known as chloasma, is an acquired pigmentary condition, occurring most commonly on the face. This disorder, which is more prevalent in females and darker skin types, is predominantly attributed to ultraviolet (UV) exposure and hormonal influences. Melasma is generally a clinical diagnosis consisting of symmetric reticulated hypermelanosis in three predominant facial patterns: centrofacial, malar, and mandibular [1]. The major clinical pattern in 50–80% of cases is the centrofacial pattern, which affects the forehead, nose, and
upper lip, excluding the philtrum, cheeks, and chin [2, 3]. The malar pattern is restricted to the malar cheeks on the face, while mandibular melasma is present on the jawline and chin. The latter is thought to occur in older individuals and may be more related to severe photodamage [4]. A newer pattern termed extra-facial melasma can occur on non-facial body parts, including the neck, sternum, forearms, and upper extremities [5]. Though common, the management of this disorder remains challenging given the incomplete understanding of the pathogenesis, its chronicity, and recurrence rates. In addition to traditional treatments for melasma, there are also promising new treatments, including topical, oral, and procedural therapies. This review will provide an up-to-date overview of the current literature on melasma, including clinical diagnosis, pathogenesis, and treatments including discussion of new topical, oral, and procedural therapies. This article is based on previously conducted studies and does not involve new studies of human or animal subjects performed by the authors.

Diagnosis

Morphologically, melasma presents as symmetric reticulated hyperpigmented patches with irregular borders on the centrofacial region, malar cheeks, mandible, and rarely upper chest and extremities. While melasma is known to more commonly affect darker skin types, it can occur in all skin types [2, 3, 6]. On dermoscopic examination, it is possible to see pronounced hyperpigmentation in the pseudo-rete ridges of the skin [7]. Using a Wood’s lamp, the hyperpigmentation can be accentuated when the pigment is epidermal [8]. However, this accentuation may be seen with dermal or mixed melasma [1, 9]. Reflectance confocal microscopy (RCM) has also been used to evaluate melasma on a cellular level. In the epidermis, it has shown an increase in hyperrefractile cobblestoning cells which corresponded to hyperpigmented basal keratinocytes on histology [10]. In some patients, epidermal dendritic cells can also be found corresponding to activated melanocytes. In the dermis, RCM may show plump bright cells corresponding to melanophages as well as solar elastosis and blood. RCM is a non-invasive technique that detects pigmenitary changes in melasma at a cellular level resolution [10]. The differential diagnosis for melasma includes lichen planus pigmentosus, discoid lupus erythematosus, phototoxic dermatitis, erythema dyschromium perstans, phytophotodermatitis, pigmented contact dermatitis, drug-induced pigmentation, poikiloderma of Civatte, erythromelanosis follicularis faciei, ochronosis, hori’s nevus, argyria, nevus of ota, lentigines, ephelides, macular amyloidoses, and post-inflammatory hyperpigmentation [11].

Epidemiology

Various epidemiologic studies have estimated the prevalence of melasma in the general population at 1% and in higher-risk populations at 9–50% [12–15]. These wide ranges are secondary to variations in prevalence among darker skin types, different ethnic heritages, and different levels of UV exposure within various geographic locations. As such, the true prevalence across the entire population is unknown. The age of onset is also unknown, with average age ranging between 20 and 30 years [3, 8]. One study argued that patients with mandibular melasma have an older age of onset in their 40s [4].

Many studies have attempted to calculate the prevalence and incidence of melasma from data available in dermatology clinics. However, this approach may underestimate the number of affected individuals given that some patients with milder disease may forgo clinical evaluation, as well as the potential for misdiagnoses. A prospective telephone-based study in a community of Latino women in the southwestern United States found a prevalence of 8.8% amongst 500 interviewed individuals [14]. Another prospective study on melasma prevalence in a New York City dermatology private practice found a prevalence of 8.2% amongst 1000 Latino patients [16]. Globally, the prevalence of melasma has also varied. A study of 3298 people in Saudi Arabia revealed a 2.9%
prevalence, compared to a prevalence of 13.4–15.5% seen in an Arab-American population in Michigan [17, 18]. Additionally, a retrospective study in a health center in Ethiopia demonstrated a 1.5% prevalence [19].

Studies have shown that melasma has a female predominance [6, 8, 20]. Although the general accepted female to male ratio is 9:1, a more recent large, multicenter study of 953 melasma patients in Brazil found a 39:1 ratio [6, 20]. An Indian study of 312 patients with melasma found a 4:1 female to male ratio [8]. During pregnancy, the prevalence likely increases, which was seen in a cross-sectional study in Tehran with a 15.8% prevalence amongst pregnant women. Similarly, in a randomly selected sample of 2000 pregnant women in India, there was a 50.8% prevalence [12, 13]. Fewer studies have been carried out on men with melasma, but they clinically tend to exhibit similar clinical features and exacerbating factors [21]. Two major risk factors found in Indian and Latino men include sun-exposure and outdoor work [21, 22].

Pathogenesis

The etiology of melasma is multifactorial. UV light has been shown in clinical and laboratory studies to trigger and exacerbate the condition [8]. UV light is thought to induce reactive oxygen species (ROS) by activating inducible nitric oxide and promoting melanogenesis [23]. Patients with melasma have also been found to have higher markers of oxidative stress when compared to healthy volunteers [24]. More recently, the role of visible light in inducing pigmentation has been appreciated. A seminal study showed sustained pigmentation from visible light in darker skin types over 2 weeks compared to pigmentation from UVA-1 light [25]. Another study showed that visible light at a wavelength of 415 nm can cause increased pigmentation that could last for 3 months [26].

The process of melanogenesis after UV and visible light exposure can be stimulated by keratinocytes and fibroblasts. One major pathway of both UV- and visible light-induced pigmentation is the secretion of stem cell factor (SCF), the ligand for the tyrosine kinase receptor, c-kit, which leads to downstream effects on the proliferation of melanocytes [27]. A recent study showed the increased expression of SCF in the dermis and c-kit in the epidermis in areas of melasma [27]. This is further supported by increased mRNA levels of melanogenesis-associated genes [28]. Other studies have found increased levels of Wnt signaling-related genes, which is notable since Wnt has been linked to the proliferation of melanocyte stem cells [28, 29]. Additionally, vascular endothelial growth factor (VEGF), a product of keratinocytes after UV damage, can sustain human melanocytes in tissue culture [30]. This is proposed as one of the mechanisms for the increased activity of melanocytes in melasma [30, 31]. Recent gene and protein expression studies have also shown down-regulation of lipid metabolism-associated genes in lesional skin, which may suggest impaired barrier function as contributing to the pathogenesis of melasma [28].

Family history is also known to be an important risk factor for developing melasma, strengthening the hypothesis of a genetic predisposition to the condition. Some studies have reported that 55–64% of patients with this condition have a positive family history [12, 32, 33]. No genome-wide study has been performed to examine associated genes, but current findings would suggest that the genes responsible involve pigmentary, inflammatory, hormonal, and possibly vascular responses. Patients with Fitzpatrick skin type (FST) II and III are less likely to have a positive family history than patients with darker skin types (IV–VI) [6, 34].

Hormonal influences play a significant role in the pathogenesis of melasma as seen by the increased prevalence with pregnancy, oral contraceptive use and other hormonal therapies [2, 3, 33, 34]. Extra-facial melasma has also been associated with a peri-menopausal state [5, 6]. An immunohistochemical study of the epidermis and dermis of affected and unaffected neighboring skin found significantly increased expression of the progesterone receptor in the epidermis of affected skin [35]. There was also increased estrogen receptor protein expression
in the dermis and around the blood vessels, which is currently of unknown significance [36].

Melasma has not been consistently associated with other clinical conditions. In a case–control study, melasma was shown to be associated with an increased number of lentigines and nevi [32]. Endocrinological conditions, such as thyroid disease, have also been investigated as having an association with melasma, but observed prevalence of thyroid diseases in these studies are not increased when compared to the general population [8, 37].

**Histology**

Historically, melasma has been classified as having three histologic variants: epidermal, dermal, and mixed [1]. In the epidermal type, there is increased pigment throughout the layers of the epidermis, particularly in the basal and suprabasilar layers. Melanocytes in the epidermis are generally enlarged, have prominent dendrites, and increased melanosomes [9, 38]. Although one study suggested an increase in melanocyte number, most studies report no change in the number of epidermal melanocytes [38]. Epidermal pigmentation may be accentuated with a Wood’s lamp which may help distinguish epidermal and dermal subtypes. The dermal subtype has melanophages in the superficial and deep dermis. Additionally, a lymphohistiocytic infiltrate may be seen in the dermis in areas with increased melanin deposition. Dermal findings can also include solar elastosis and an increase in blood vessels [9, 11]. Mixed melasma often displays combined histologic features of the epidermal and dermal subtype.

**Clinical Assessment and Psychosocial Implications**

Given the variability of presentation, assessing melasma severity can be challenging. Several validated tools have been created to evaluate both the clinical appearance and the psychosocial impact of dyspigmentation from melasma. Moreover, these standardized tools have enhanced the ability to assess therapeutic efficacy of various melasma treatments in clinical trials. The Melasma Area and Severity Index (MASI) is a validated scale used to measure the extent of facial hyperpigmentation. This is a numeric score calculated as an area-weighted score of pigmentation and homogeneity located on the forehead, chin, right and left malar cheek [39]. After eliminating homogeneity from the calculation due to the decreased interrater reliability of that metric, the modified MASI (mMASI) was created [39]. It has now been correlated to the Melasma Severity Score, which is a global score that incorporates both objective data and patient’s subjective assessment. It is now used in clinical trials [40].

For many dermatologic conditions, a health-related quality of life (HRQoL) tool has been used to measure the psychosocial aspects of skin diseases. Balkrishnan and colleagues created the Melasma Quality Of Life Scale (MELASQOL), a validated modified version of the HRQoL [41]. The scale consists of 10 questions pertaining to the quality of life and impact of the disease rated on a Likert scale. Other psychometric scales that can be used in those with melasma are the Dermatology Life Quality Index (DLQI) and the SKINDEX-16 [42–46].

**Treatment**

Treatments for melasma include topical, oral, procedural, and combination treatments. These are aimed at various aspects of the pathogenesis of melasma including photodamage, inflammation, vascularity, and pigmentation (Table 1).

**Topical**

Topical treatments, including photoprotection, are typically the first-line therapies for melasma. The most common therapeutic agents used are those that inhibit the production of melanin through melanogenesis and melanocyte proliferation. Concomitant use of various topical therapies with different mechanisms of action are preferred to monotherapy.
Photoprotection

UV and visible light avoidance are critical to prevent flares and exacerbation of melasma. In repeated randomized-controlled studies with 40–60 subjects, a comparison of broad-spectrum UVA and UVB filters combined with visible light blockers, such as iron oxide, versus broad-spectrum UV filters alone showed reduced melasma relapses in the former group [47–49].
**Hydroquinone**

Hydroquinone (HQ) has historically been the most studied topical agent in the treatment of melasma. This compound works by inhibiting tyrosinase, which prevents the conversion of DOPA to melanin [50]. Others have postulated that it can also directly lead to melanocyte destruction and melanosome degradation. In several studies, the use of HQ 4% has led to a statistically significant improvement of melasma dyspigmentation [46, 51]. Although very effective and dosed at different strengths, it can cause an irritant dermatitis in some individuals and chronic use can lead to exogenous ochronosis [7].

**Corticosteroids**

Corticosteroids can prevent pigmentation by non-selective suppression of melanogenesis while also serving as an anti-inflammatory agent [52]. Corticosteroids alone are unlikely to be superior to depigmenting agents when used as monotherapy [52]. Although they have an independent ability to suppress melanogenesis, the current literature shows that corticosteroids have not been demonstrated to have long-term benefits in treating melasma [50]. Moreover, long-term steroid use may lead to telangiectasias, acne, epidermal atrophy, striae, and hypopigmentation.

**Retinoids**

Topical retinoids have also been effective in treating melasma, with a postulated mechanism of promoting keratinocyte turnover [53]. A small but sentinel study in 1993 showed that tretinoin 0.1% cream could significantly decrease objective colorimetry measurements of melasma pigmentation [53]. Another study has confirmed the beneficial use of tretinoin 0.1% cream for the treatment of melasma in Black patients [54].

**Other Synthetic Topical Compounds**

Another tyrosinase inhibitor, 4-n-butylresorcinol, has been increasingly used in trials and has shown significant improvement in pigmentation in melasma [55, 56]. Noted adverse effects, including erythema and pruritus, were self-limited and minimal; however, long-term data on this product is lacking. Tranexamic acid, a synthetic version of lysine and a hemostatic agent, has been increasingly used in the topical, oral, and injectable forms to treat melasma. Studies have demonstrated occasional negative findings when used as a monotherapy, but increased efficacy when used in combination with other pigmentation-based therapies [57–61]. The topical formulation of tranexamic acid, however, has had limited success and less efficacy than when used in oral form. Topical flutamide, an antiandrogenic agent, has also been studied in comparison to HQ 4%, and was found to have statistically significant MASI scores and patient satisfaction; however, no difference in the mexameter melanin assay was observed between the two groups [62].

**Natural Topical Compounds**

In recent years, naturally occurring compounds have been investigated for their therapeutic activity against pigmentation. Niacinamide, which inhibits melanosome transfer to keratinocytes, has been shown to decrease pigmentation in a small study with 27 subjects [63]. Both ascorbic acid and kojic acid can inhibit tyrosinase activity and have been shown in small studies to lead to decreased pigmentation [46, 63–65]. Ascorbic acid has a theorized benefit of decreasing reactive oxygen species, which decreases inflammation in melasma lesions [23, 65]. However, both were shown to be inferior to HQ in improving MASI scores when used as monotherapies [51, 52, 66]. Another natural compound, azelaic acid (AA), was noted in an open-label study to be effective in improving pigmentation by inhibiting tyrosinase activity [43]. This compound, which is derived from the yeast, *Pityrosporum ovale*, also has anti-inflammatory effects. Adverse effects are not common, but can include burning and erythema. *Bellis perennis*, a flower extract that inhibits melanin synthesis, was demonstrated, in combination with topical licorice and emblica, another natural antioxidant, to be similar in efficacy to HQ 2% in decreasing pigmentation and inhibiting inflammation through the arachidonic acid
cascade [67]. Other topical natural compounds used, such as lignin peroxidase, arbutin, and soy, have also been used to treat melasma in small studies with favorable results [63, 68–70].

**Combination Topical Compounds**
Recent studies have shown that combination topical therapies are superior to monotherapies in efficacy [71]. Triple combination therapy (TCT) with HQ, a retinoid, and a topical steroid was the first combination topical therapy to gain United States Food and Drug Administration approval. In an investigator-blinded randomized study with 260 Asian patients, TCT with HQ 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% was superior to HQ 4% monotherapy in improving melasma [72]. Of note, about 50% of patients on TCT reported increased erythema, skin irritation, and discomfort when compared to 14% of controls. Dual therapy with tretinoin 0.1% and HQ 3% was also demonstrated to improve melasma among female Korean patients [73].

**Camouflage**
With the recurring nature of melasma and the long, challenging treatment duration, cosmetic camouflage can provide patients with another option to improve the psychosocial effects of the condition and quality of life. Cosmetic camouflage, including concealers and other pigmented cover-ups, has been shown to significantly improve the DLQI in a study of 24 patients with pigmentary disorders [74]. Several cosmetics brands offer pigmented foundations and concealers that may even skin complexion and may also include broad-spectrum UV blockers.

**Oral**
In addition to topical therapies, oral therapies are emerging as additional treatment options for this disorder. Tranexamic acid (TA), an anti-plasmin agent, decreases the generation of arachidonic acid, which leads to a reduction in melanocyte-stimulating hormone (MSH) and a decrease in pigmentation production [60]. One study showed that TA may also decrease VEGF and entothelin-1, both of which may be responsible for increasing vascularity in affected lesions [44]. While formulations of tranexamic acid have not been directly compared, recent studies generally suggest that about 90% of patients treated orally improved after 2–6 months compared to about 95% of patients treated with topical 2% preparations and who improved after 3 months [44, 60, 61]. Notable adverse effects of oral TA include abdominal bloating, headache, tinnitus, menstrual irregularities, and, rarely, deep venous thrombosis (DVT) [60]. Due to the serious risk of a DVT, screening for risk factors of thrombosis is necessary before initiating treatment. Alternative medications, such as *Polypodium leucotomos* (PL) and glutathione, have also been studied as adjunctive treatments with positive results [75–77]. PL has been shown to decrease UV-induced photodamage and inhibit ROS, which in turn decreases the T cell-mediated response that leads to increased inflammation and pigmentation in the skin [76]. In a randomized controlled trial in the Philippines, oral glutathione, a naturally occurring compound, resulted in decreased melanin when compared to those taking placebo over a 4-week period [77]. Glutathione is thought to act as an anti-oxidant that decreases inflammation [63].

**Procedural**
The recent literature on procedural melasma therapies has predominantly included case reports and case series that evaluate the use of chemical peels, microneedling, microdermabrasion, and lasers, typically in conjunction with other treatment modalities. It is important to note that many procedural studies include concomitant use of topical therapies and photoprotection [31, 78–82].

**Chemical Peels**
Chemical peels have been studied as an adjunctive treatment modality for melasma due to their ability to increase epidermal remodeling and to increase keratinocyte turnover. Chemical peels are frequently used in combination with other topical products [83]. Several studies have suggested that superficial peels may be beneficial for the epidermal-subtype of
Amongst the various peels, glycolic acid (GA) has been most extensively studied in the treatment of melasma. A small open-label study found that 30–50% GA peels at 3-week intervals for 6 months in addition to AA 20% twice-daily regimen resulted in superior MASI scores when compared to AA 20% alone [45]. However, a small split-face study found no difference in decreased pigmentation when using HQ 4% with GA 20–30% compared to HQ alone [85]. Another split-face study showed no difference in a regimen with salicylic acid (SA) 20–30% peel and HQ 4% compared to HQ monotherapy [86].

Combination peels have also been explored in recent studies. A study in India found that a combination of 20% SA and 10% mandelic acid was equally as efficacious as 35% GA over 12 weeks in significantly improving MASI scores for FST IV and V patients [42]. Trichloroacetic acid (TCA) 10–20% peels were shown to have similar efficacy to GA peels but with more adverse effects, such as burning and peeling [87].

Microneedling

Another adjunctive treatment is microneedling or mesotherapy, which creates small channels in the skin to deliver small amounts of topical drugs intradermally [56, 58, 88]. The skin punctures induced by microneedling can also stimulate a beneficial wound-healing response with fewer side effects compared to conventional resurfacing procedures [89]. This technique may result in a deeper and more even placement of the medication to the epidermis and dermis [58, 88]. In a randomized study using multiple microinjections of TA intradermally compared to cycles of microneedling alone followed by the application of topical TA, the data showed possible clinical benefit with use of microneedling but no statistically significant benefit [58]. A prospective study of patients treated with topical lightening agents, rucinol and sophora-alpha, alone compared to use of those topicals with microneedling demonstrated a significant improvement in MASI scores when administered with microneedling [56]. A limitation, however, is that the study was not blinded to either the patient or the investigator.

Laser and Light Treatments

In more recent years, laser therapy has been investigated to treat melasma with varying success. Lasers can utilize thermal energy to selectively target various chromophores in the skin. Non-ablative lasers are preferred for the treatment of melasma over ablative lasers given the tendency to cause less inflammation and subsequently less post-inflammatory pigment alteration (PIPA). Non-ablative Q-switched lasers, including the Q-switched ruby laser (QSRL) and Q-switched neodymium:yttrium–aluminium–garnet (QNd:YAG) lasers, selectively target the chromophore melanin [50]. When used as monotherapy, neither QSRL nor QNd:YAG have been found to have long-term benefits in treating melasma [80, 90–92]. However, one small study found that using low-dose fractional QSRL significantly decreased MASI scores [78]. More recent studies have found improvement in pigmentation with low fluence QNd:YAG, although the patients also applied sunscreen, HQ, tretinoin, or ascorbic acid after laser treatment [93, 94].

Intense pulsed light (IPL), has also been used successfully in several smaller studies for the treatment of melasma as a monotherapy and in combination with QSRL [95]. Fractionated IPL monotherapy used for melasma maintenance treatment resulted in improvement in mMASI scores over 14 weeks [95]. Some authors postulate that repeated IPL treatments may promote the upward shedding of the melanosomes destroyed by QSRL [80, 96]. Therefore, they suggest that combined IPL and QSRL therapy may decrease the risk of post-inflammatory hyperpigmentation (PIH) and therefore may also require more treatment sessions.

Other ablative lasers, such as carbon dioxide (CO₂), erbium:YAG (Er:YAG), and non-ablative fractional lasers, have also been used with varying success to treat melasma [50, 79, 81]. CO₂ lasers have been used in clinical trials with Q-switched alexandrite lasers, but have been repeatedly found to be associated with PIH, especially at the periphery of lesions [97, 98].
recent split-face study using low-power CO₂ laser versus QNd:YAG showed improved mMASI scores on the CO₂ arm without a significant difference in adverse effects [99]. Er:YAG laser has also been shown in a small study with 20 patients to improve pigmentation using MASi scores, but recurrence was observed at 3—4 months [82]. Two studies that utilized a fractional nonablative 1550-nm erbium-doped fiber laser demonstrated improved pigmentation in about 60% of patients using investigator-created metrics [79, 81]. Neither study demonstrated long-term complications.

Other energy sources, such as monopolar radiofrequency (RF), have been used to treat melasma. RF causes cellular biostimulation, intracellular oxygenation, and vasodilatation [100]. In a prospective study of 50 patients, monopolar RF was used to deliver kojic acid with improved MASi scores and decreased inflammation, but there were no controls using only topical therapy, thus limiting data interpretation [100].

With increased recognition that inflammation and angiogenesis may play a role in the pathogenesis of melasma, a copper bromide anti-angiogenesis laser was evaluated in four Korean women who received 4 treatments over 8 weeks. Treatment was found to significantly decrease the MASI score and decrease endothelin-1 and VEGF on immunohistochemistry [31].

CONCLUSIONS

Melasma continues to be a frustrating condition to treat and one with significant psychosocial implications. Treatment efficacy can vary due to several factors including variability in clinical presentation and response to treatment amongst different genders, skin phototypes, and ethnicities. Given the multifactorial etiology of melasma, it is important to have a multimodal therapeutic approach that addresses factors such as photoprotection, inflammation, vascularity, pigmentation, and hormonal influences. New research continues to increase our understanding of melasma and how it can be best treated. The past decade has seen the emergence of new topical, oral, procedural, and combination therapies. Greater understanding of the pathogenesis of melasma will help in the development of future treatments for this common, yet challenging, condition.

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