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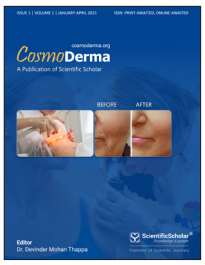

Review Article

Current updates on melasma treatments

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ABSTRACT

Melasma is a common chronic relapsing pigmentary disorder primarily affecting women. It is highly prevalent in the Indian skin type with a large psychological impact. Treatment is challenging with no cure available yet. Even so, treatment modalities are many and varied-each promising more than the last. We analyzed the understanding of photoprotection, topical and oral treatments, and procedures such as microneedling, laser resurfacing, and peelings that serve as the primary methods for controlling and preventing this illness. While there are a few well established treatments such as hydroquinone and triple combination creams, side effects impede their long-term use. Safer alternatives have now come up which can be used for extended durations such as kojic acid, rucinol, and cysteamine cream. Lasers and light therapies have slowly become an essential component of melasma management. In this manuscript, we attempt to provide a critical and concise review of the current updates in melasma therapy.

Keywords: Melasma, Updates, Lasers, Peels

INTRODUCTION

Melasma is a common chronic relapsing pigmentary illness that affects photoexposed areas, particularly in women of reproductive age. Its pathophysiology is complicated and includes the interaction of several factors, including genetic predisposition, ultraviolet (UV) light, hormonal changes, and drug intake. The majority of patients with melasma have a chronic condition with seasonal variation and relapses after effective therapy, necessitating post-treatment care. Melasma caused by pregnancy or photosensitizing medicines has a better prognosis if the causative factor ceases. Recent research has shed light on other variables that might be involved in the pathophysiology of melasma. They include numerous genetic and vascular growth factors, as well as the function of the genes H19, inducible nitric oxide synthase (iNOS), and Wnt pathway modulator genes. The melanocortin type 1 receptor (MC1R) is the most powerful regulator of eumelanogenesis. It is encoded by a highly polymorphic gene that is responsible for multiple phenotypes of skin and hair colour, as well as skin sensitivity to ultraviolet radiation. Studies have found increased polymorphism of MC1R gene in melasma patients.[1] Till date there is no curative therapy for melasma which especially concerns the Indian skin type.

SUN PROTECTION

Direct sun exposure is one of the main risk factors for melasma as reported by a Tunisian study wherein 51% of women recognized it as a triggering factor.[2] Visible light (VL) should be avoided in melasma patients in addition to the standard ultraviolet A (UVA) and ultraviolet B (UVB)

protection because shorter wavelengths of visible light (blue light) encourage hyperpigmentation through opsin 3 in melanocytes.[3] For patients with melasma, behavioural strategies and self-awareness toward sun exposure should be emphasized as majority of sunscreens underperform in real life due to the low amount of product used or insufficient reapplications, especially for UVA and VL protection.[4] The primary waveband which should be addressed during melasma treatment and maintenance after treatment is UVA. A study performed in India studied the therapeutic benefit of sunscreen as a sole agent in treating melasma and found that the mean Melasma Area and Severity Index (MASI) reduced from 12.38 ± 14.7 to 9.15 ± 4.7 and the participants also reported a better quality of life.[5] Tinted sunscreens contain iron oxide and are known to provide protection against visible light apart from being cosmetically more acceptable. Physical sun protection tools such as hats, visors, umbrellas, and scarves can also be beneficial. Oral photoprotecting agents like *Polypodium leucotomos* extract have been studied and are known to have uniform, total body surface protection. They are a useful adjunct in melasma.[6]

PHARMACOLOGICAL THERAPIES

1. Topical hydroquinone (HQ) – HQ is a phenolic compound with antioxidant properties that inhibits tyrosinase, thereby interfering with melanogenesis. It also inhibits DNA and RNA synthesis and can alter the formation of melanosomes, damaging melanocytes selectively. It is considered to be gold standard for therapy in melasma. A statistically significant decrease in MASI score was observed for both agents in a small, recent double-blinded randomized controlled trial (RCT) study, which involved 20 patients receiving either liposomal HQ alone or HQ 4% once daily for 12 weeks.[7] Since HQ has many undesirable side effects such as irritant contact dermatitis, exogenous ochronosis, colloid milium, and paradoxical post-hyperpigmentation among others, the use of liposomal formulation can attenuate these without compromising the efficacy of HQ.
2. Triple combination cream – In 1975, Kligman and Willis first discussed using a combination of 0.1% tretinoin, 5% HQ, and 0.1% dexamethasone to lighten skin.[8] At present, a triple combination cream that contains 4% HQ, 0.05% tretinoin, and 0.01% flucinolone acetonide is Food and Drug Administration approved. In addition to having a hypopigmentary impact, retinol has an anti-aging effect. Steroids prevent the release of the anti-inflammatory agents endothelin-1 and granulocyte-macrophage colony-stimulating factor, which are produced in response to photodamage and melanogenesis and work to reduce mild inflammation.[9] In 28 weeks, multicenter RCTs, 641 patients were assessed and three dual combination agents made up of tretinoin (RA) + HQ, RA + fluocinolone acetonide (FA), and HQ + FA were compared to a hydrophilic triple combination (TC) cream (HQ 4%, RA 0.05%, FA 0.01%). Compared to 30% of patients treated with dual combination, >70% of patients treated with TC cream had a pigmentation reduction of 75%.[10] The use of these creams is efficacious and safe when used intermittently not beyond 6 months. Side effects could be erythema, scaling, pruritus, atrophy, telangiectasias, etc.
3. Kojic acid (KA) – Due to its effects for whitening skin through chelating divalent ions, capturing free radicals, and blocking tyrosinase, it is being explored as a cosmeceutical product. Moreover, it contains anti-bacterial, anti-inflammatory, anti-proliferative, and anti-phototoxic effects.[11] KA is used in concentrations ranging from 1% to 4% alone or in combinations with other lightening ingredients. After 2–4 weeks of consistent use, its effects begin to appear and they get better during the following 6 months.[12] From week 4 to week 12, two groups of 60 patients treated nightly with HQ 4% cream or a KA combination cream (KA 0.75% and ascorbic acid 2.5%) showed a reduction in MASI score. However, the 4% HQ cream was superior to the KA cream as a lightening agent.[13]
4. Azelaic acid (AZA) – Derived from the fungus *Pityrosporum ovale*, it is a tyrosinase inhibitor of melanocytes and mitochondrial oxidoreductases that reduce DNA synthesis in both normal and hyperfunctioning melanocytes. It is used in a concentration of 20% for melasma patients as an adjuvant to other therapies. The efficacy of AZA 20% cream for treating melasma was compared to HQ 4% cream in a 24-week, multicenter, controlled, and double-blinded clinical trial with 329 women. There was no significant difference between the two treatments; 65% of patients treated with AZA 20% had good to excellent results, compared to 73% of patients treated with HQ 4%.[14] The main advantage of AZA is its safety in pregnant and lactating women with side effects limited to burning or tingling sensation after application.
5. Arbutin – Arbutin, an HQ derivative similarly presents in the leaves of blueberries and cranberries, is derived from the grape *Uva ursi folium*. The consensus on the mechanism by which arbutin prevents the synthesis of melanin in cells is that it prevents the catalytic activity of tyrosinase that has already been expressed or irreversibly inactivates it rather than inhibiting the fresh synthesis of tyrosinase.[15] A randomized placebo-controlled double-blind trial was done in 2015, wherein participants with melasma and solar lentigines were advised to apply extract of leaf of five-leaf serratula containing 2.51% arbutin for 8 weeks. Lightening was observed in

75.86% of the patients with *melasma*.[16] Arbutin should be combined with other active substances that have different mechanisms of action to maximize its skin-lightening effectiveness as opposed to being used alone. Nanoemulsions,[17] nanoparticles,[18] and microneedles[19] containing arbutin have been developed as well.

6. Niacinamide – It is the biologically active form of niacin (Vitamin B3). Niacinamide decreases melanin accumulation in the skin by downregulating melanosomes transferred from keratinocytes to melanocytes. It also attenuates inflammation and solar damage.[20] A double-blind and split-faced study was done on 27 patients wherein patients applied 4% HQ on one side of face and 4% niacinamide on the other side for 8 weeks. Efficacy of niacinamide was 62% reduction in MASI compared to 77% reduction for HQ. Moreover, side effects such as erythema, pruritus, and burning sensation were milder for niacinamide.[21] Topical niacinamide is safe for pregnant and breastfeeding women as well. It can be used as a 4–5% cream alone twice daily or in combination with other lightening agents.
7. Ascorbic acid – Ascorbic acid binds to copper, inhibiting the enzyme tyrosinase. This reduces oxidative polymerization of melanin precursors, which prevents the synthesis of melanin in the melanogenesis pathway.[22] It also reduces dermal damage, promotes collagen synthesis, and has antioxidant and photoprotective effects. Studies have shown efficacy of topical L-ascorbic acid in reducing MASI scores with limited side effects as compared to HQ 4%. Intradermal ascorbic acid has also been used to treat melasma. In a split face study, 24 patients with melasma were treated with intradermal tranexamic acid (TXA) and ascorbic acid on one side and TXA and placebo on the other. There was a significant decrease in MASI scoring at the end of 8 weeks in both groups with the ascorbic acid group showing greater decrease than placebo.[23]
8. TXA – Topical, intradermal, and oral TXA formulations have all been studied for the treatment of melasma. The molecule is an antifibrinolytic agent that inhibits UV-induced plasmin activity in keratinocytes. It does so by preventing the binding of plasminogen to the keratinocytes. This results in less free arachidonic acid and a diminished ability to produce prostaglandins, and this decreases melanocyte tyrosinase activity.[24] All research has found greater efficacy of oral TXA than creams or injections. Topical TXA has been used in concentrations ranging from 2% to 10%. Sixty women with melasma participated in a double-blinded RCT to compare the effectiveness of TXA 5% cream with HQ 2% cream when used twice daily for 12 weeks. MASI score improved in both groups, but there was no discernible statistical difference between them. The side effect profile was better for TXA.[25] A split-face and controlled trial of 49 individuals compared intradermal TA to HQ cream. After 24 weeks of twice-daily HQ or biweekly TA injections, there was no substantial difference between the treatments as per MASI scoring.[26] A RCT was done wherein 45 women with melasma were divided into three different groups, treated with oral TXA 250 mg twice daily, intradermal 100 mg/mL TXA, and 40 mg/mL TXA, respectively. The study found a significant decrease in mMASI scores in all three groups at the end of 8 weeks, but no statistically significant difference was found among the treatment groups. There is, however, little information on how long the reduction in modified melasma area severity index (Mmasi) scores lasts after injection, and maintenance therapy may be required to maintain effects.[27] Several research papers have reported excellent improvement in melasma with oral TXA-given in a dose of 250–500 mg twice a day. A recent randomized open label study divided 50 patients with melasma in two groups with one group receiving 250 mg twice a day and the other receiving 500 mg twice a day. Both groups showed a significant reduction in mean mMASI at the end of 12 weeks. mMASI remained stable at the end of the 12 weeks follow-up period demonstrating the comparable effectiveness of both dosing regimens of oral TXA. Hence, low dose is a good option for persons with risk factors of thrombosis.[28] The most successful formulation was thus found to be oral TXA, particularly in cases of resistant melasma; nonetheless, it irritated many patients' gastrointestinal systems and disrupted their menstrual cycles. When prescribing this medication to patients, the pro-thrombotic characteristics of the medication must be considered. Effective alternatives to oral therapy include intralesional injections and topical TXA microneedling. Ultimately, topical TXA used alone was discovered to be the least effective approach; however, results can be improved when combined with other cosmeceuticals. The standard topical melasma medication HQ was shown to be less tolerated than topical TXA.
9. 4-n butylresorcinol – Also known as rucinol, itinhibits the activity of tyrosinase and tyrosinase related protein-1. These are essential enzymes in melanogenesis. 23 melasma patients participated in a randomized controlled split-face experiment to assess the efficacy and safety of liposome-encapsulated 4-n-butylresorcinol 0.1% cream. On the treatment side, a statistically significant decrease ($P = 0.043$) in the melanin index was detected.[29] Rucinol is used in combination with other skin lightening agents for better results.
10. Metformin – Metformin reduces intracellular cyclic adenosine monophosphate accumulation, which

inhibits melanogenesis; however, due to its low lipophilicity, it must be used in high concentrations for topical efficacy.[30] Forty Egyptian patients with melasma participated in a randomized controlled trial that compared topical metformin 30% lotion twice daily to TC for 8 weeks.[31] MASI dropped by 56% and 57%, respectively. Another study from Egypt also reported improvement in MASI score on usage of compounded topical metformin 30% for 2 months.[32]

11. Pycnogenol – A standardized extract called pycnogenol is taken from the *Pinus pinaster* bark. It has condensed flavonoids (procyanidins) and monomeric phenolic compounds (catechin, epicatechin, and taxifolin), which have antioxidant and anti-inflammatory properties and can promote the production of NOS and inhibit the melanin biosynthesis process.[33] In a randomized controlled trial, 44 melasma-afflicted women were given 150 mg of oral pycnogenol (or a placebo) along with TC and a broad-spectrum tinted sunscreen. At 60 days, the group taking oral pycnogenol reduced mMASI more effectively, at 49% versus 34%.[34]
12. Thiamidol – It has been found to be a potent inhibitor of human tyrosinase. *In vitro* studies have reported a superior depigmenting activity compared with HQ.[35] Twenty-three women with facial melasma had a mean MASI reduction of 26% after receiving thiamidol 0.2% twice daily for 24 weeks.[36] In an RCT, twice daily thiamidol 0.2% was compared with HQ 4% in 50 female patients. At 90 days, the mean reduction in of MASI score was 43% and 33%, respectively.[37]
13. Malassezin – Malassezin is a natural indole compound produced by *Malassezia furfur*, a fungus that has been shown to induce melanocyte apoptosis, the induction of apoptotic markers in a dose-dependent manner, and decreased melanin synthesis in melanocyte cultures. A proof-of-concept, 22-week double-blind study, assessed the efficacy of topical malassezin in 20 patients of melasma for 14 weeks with a follow-up of further 8 weeks. Patients received a 0.1–1% oil-in-water emulsion to apply. The lightening effect of the compound was seen as early as 2 weeks with no relapse for 8 weeks after treatment.[38]
14. Glutathione – Tripeptide glutathione which contains glutamate, cysteine, and glycine works in a number of ways to produce a skin-lightening effect. It is an endogenous antioxidant, inhibits tyrosinase, is anti-inflammatory and alters production from eumelanin to pheomelanin. Since the ratio between the black or brown eumelanin and yellow-red pheomelanin determines skin color, there is a lightening impact.[39] Glutathione has gained worldwide popularity as a skin whitening ingredient and is used orally, topically as well as through intravenous route. Studies have found reduced levels of plasma glutathione in melasma patients compared to controls.[40] A double-blind RCT compared the combination of oral and topical glutathione in 47 participants and found better results as compared to monotherapy.[41]
15. Cysteamine – L cysteamine is a biological antioxidant which has depigmenting properties. Its efficacy has been revealed in a few randomized trials. Fifty patients were evaluated in a double-blind RCT to compare the efficacy of cysteamine 5% (applied daily for only 15 min) versus a modified Kligman's formula (MKF: HQ 4% + RA 0.05% + betamethasone 0.1%) applied nightly for 16 weeks. At weeks 8 and 16, the cysteamine treatment resulted in a MASI score reduction comparable to the MKF-treated group that was statistically significant. The cysteamine cream also had the advantage of being better tolerated.[42]
16. Methimazole – Due of its ability to reduce pigmentation by blocking peroxidase, the oral antithyroid medication methimazole has gained popularity recently. It is used topically in melasma as a 5% cream. In this formulation, it does not produce any significant alterations in thyroid function.[43] An RCT compared the efficacy and safety of 4% HQ cream with 5% methimazole cream in 50 patients. At the end of 8 weeks, MASI score reduction was more in the HQ group than methimazole group, but relapse rate was also higher in this group. Methimazole 5% cream represents an alternative treatment in melasma by virtue of its non-cytotoxic and non-mutagenic properties.[44]

CHEMICAL PEELS

Chemical peels are not considered first-line therapy, but rather an adjuvant measure. Importantly, superficial peeling in serial sessions should be conducted for melasma. The effects are dependent on keratinocyte turnover and melanin distribution.

1. Glycolic acid – This is the most widely used and extensively studied peeling agent for melasma. Glycolic acid peels in the strength of 30–70% are used in serial sessions to achieve good results. Multiple studies have reported satisfactory improvement with the use of glycolic acid peels in combination with topical agents for melasma.[45] In an Indian study conducted in 15 female patients with melasma, 50% glycolic acid peel was performed once a month for 3 months. MASI improved in 91% patients which was statistically significant.[46]
2. Trichloroacetic acid (TCA) – Applied in 10–35% concentrations at the most, TCA peel is less frequently preferred in darker skin types due to the risk of scarring and post-peel dyschromias. At these concentrations, it reaches only up to upper papillary dermis and hence cannot treat mixed or dermal melasma. In a comparative study on 40 Indian women with melasma, the reduction

in MASI post 6 TCA peels was similar to that observed with 10–35% glycolic acid peels. However, the TCA group complained of more severe burning and post-peel crackening.[47] This highlights the caution required in using TCA peels for darker skin types.

3. Salicylic acid – 10–30% salicylic acid is a superficial peeling agent occasionally used for melasma. An RCT evaluated the efficacy of adding serial 20–30% salicylic acid peel every 2 weeks in 20 women with melasma being treated with twice daily 4% HQ. Salicylic acid peeling was not found to be more effective than HQ cream alone.[48]
4. Jessner's solution – Recent interest in Jessner's solution is in combination with glycolic acid and TCA. In a study of 20 female patients with melisma, a combination of modified Jessner's solution with 15% TCA was compared with only 15% TCA, and it was found that the result was better on the side of the combination peel.[49]
5. Lactic acid – Lactic acid is an old but innovative agent for peeling and it has similar activities like glycolic acid. Twenty patients with facial melasma were enrolled in a study to test the efficacy of 82% lactic acid peel every 2 weeks. At the end of the 12 weeks, MASI score reduction was statistically significant.[50] Lactic acid was also compared with Jessner's solution in a split-face design, and similar improvement was seen on both the sides with no relapse at a follow-up after 6 months.[51]
6. Tretinoin – The mechanism of action of tretinoin peels is proposed to be similar to that of topical tretinoin, that is, through changes in the epidermis and dispersion of melanin. Slow-release peels with 5–10% tretinoin serve to lighten epidermal pigment, lessen photodamage, and enhance skin texture.[52] Ten female melasma patients were enrolled in a 12-week open left-right comparison study. Half of the face received a 1% tretinoin peel, and the other received weekly applications of 70% GA. The decrease in MASI with the tretinoin peel at 6 and 12 weeks was comparable to that attained with the regular glycolic solution, with relatively minor side effects.[53]

LASERS AND LIGHT THERAPIES

The use of laser and light technologies to treat melasma has been investigated in numerous clinical trials. Intense pulsed light (IPL), fractional 1550-nm non-ablative laser, pulsed dye laser (PDL), copper-bromide laser, and Q-switched neodymium-doped yttrium aluminium garnet laser (QS Nd: YAG) have all demonstrated successful outcomes. In routine clinical practice, the laser that targets melanin most used for treating melasma is the QS Nd-YAG in toning mode. Laser toning technique using a collimated, low-fluence, and 1064-nm Q-switched Nd:YAG laser (QSNYL) removes melanosomes and damages the dendrites of melanocytes without destructing the whole melanocytes by a process called "subcellular selective photothermolysis."[54] A study done on 21 Caucasian women with melasma showed excellent results with this technique as per mean reduction of mMASI score.[55] The recently launched picosecond lasers have their pulse duration in picoseconds. The energy, delivered in an even shorter time, reduces the photothermal effect and increases the photoacoustic effect in the treated tissue. Picosecond lasers may be more effective than nanosecond lasers in treating melasma, but this is not yet fully established. Split-face treatment was administered to 12 patients over the course of four sessions spaced 1 month apart. Each patient's face was treated with a 1064 nm QS-Nd: YAG laser on one side and a 755 nm picosecond laser on the other. More clearance was seen at the 755 nm picosecond laser side than the 1064 nm QS-Nd: YAG side during the 3-month follow-up.[56] Since PDL is the gold standard for vascular lesions, it can target the vascular component of melasma.[57] In IPL, the absorption of light by melanin results in thermolysis. A study found excellent results in 47% and good results in 29% patients of melasma with IPL. Since the non-coherent light targets all pigment in the skin, there are chances of damage to normal perilesional skin. IPL is thus not recommended in patients with darker skin tones.[58] The 1927 nm thulium device is one non-ablative laser that shows promise for treating melasma since it penetrates close to the dermal-epidermal junction.[59]

MICRONEEDLING

The exact workings of microneedling in melasma are not yet fully understood. Early keratinocyte proliferation that increases melanin transcutaneous removal happens after the procedure. Moreover, microneedling repairs damaged basal membranes and improves skin photoaging. It can be used to enhance treatment outcomes for many topical agents such as topical TXA, vitamin C, platelet-rich plasma, non-HQ-based depigmentation serums, and HQ-based depigmenting agents among others. The decrease in melasma severity was large with the peak effect seen at 12 weeks as per a systematic review.[60]

CONCLUSION

Melasma is a complex disorder with many challenges to treatment. No single treatment modality has been found to give complete clearance in all individuals. As our understanding of the pathogenesis of melasma develops, new therapeutic targets are discovered which require proper evaluation via RCTs before they can come into widespread usage. To select a course of treatment that is appropriate for the degree and type of melasma, knowledge of the exact mechanism of action of the medications listed above is necessary. The first line of therapy is strict daily sun

protection and pairing topical bleaching chemicals with tinted sunscreen, which may affect melanogenesis differently. HQ and triple combination creams remain gold standard but in view of their adverse effects, adjuvant therapies such as TXA, KA, niacinamide, and thiamidol can be used for maintenance. Procedures are an important tool in the arsenal of melasma therapy and combining microneedling, lasers with standard therapy can give superior results.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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