Hyperpigmentation in Darker Skin Types:

A Review of Current Treatments



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>>Pigmentary disorders are a leading concern for patients and consumers worldwide. Common disorders of hyperpigmentation resulting from the overproduction, transfer, and/or deposition of melanin include inflammation-associated hyperpigmentation (IAH) also known as post-inflammatory hyperpigmentation (PIH), melasma, and lentigines. IAH occurs as a result of injury or inflammation in the skin. IAH can occur in all skin types, but it is more common in patients with skin of color.[1,2] Melasma, formerly known as chloasma, is a chronic, acquired disorder of hyperpigmentation. It presents with symmetric, tan to dark brown, reticulated patches commonly involving the malar cheeks, forehead, and upper lip.[3] Historically, melasma has been classified as epidermal, dermal, or mixed based on the depth of involvement. These findings can be elucidated by Wood's lamp examination. Epidermal melanin appears tan to brown and is accentuated by Wood's lamp. Dermal melanin appears blue-gray and does not react to Wood's lamp. Examination by confocal microscopy often reveals a mixed pattern. The etiology of melasma is not fully understood. Evidence suggests that photoaging and solar elastosis are predominant features of melasma.[4] A complex interaction between intrinsic factors (genetic, hormonal), extrinsic factors (environmental, UV radiation), and skin cells (melanocytes, keratinocytes, fibroblasts, and endothelial cells) results in the excessive production of melanin. Histopathologic features include degradation of the basement membrane, solar elastosis, ectatic vessels, and increased numbers of mast cells.[5] Lentigines are a common sign of photoaging characterized by tan to brown, sharply demarcated macules on sun-exposed areas such as the face and back of the hands.

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While they can occur in all skin types, they are more common in Fitzpatrick skin types I-III.[6]

The differential diagnosis of facial pigmentary disorders is broad and includes pigmented contact dermatitis (Riehl Melanosis), drug-induced hyperpigmentation, lichen planus pigmentosus, exogenous ochronosis, acquired bilateral nevus of Ota-like macules (Hori's Nevus), and facial acanthosis nigricans. Before initiating treatment of facial pigmentary disorders, an accurate diagnosis must be made by obtaining a thorough history, including potential exposures and past medical history, and performing a detailed physical examination. The use of diagnostic tools such as dermoscopy, Wood's lamp, and biopsy may be necessary.

Although pigmentary disorders are often considered cosmetic, studies demonstrate how significantly they can impact a patient's quality of life and mental health.[7] Given the refractory and recurrent nature of pigmentary disorders, optimal treatment may require a multifaceted approach including oral, topical, and procedural interventions.

SUN PROTECTION

Sun protection plays a vital role in the treatment of facial pigmentary disorders as it helps prevent further darkening of existing pigmentation and reduces the risk of developing

new areas of hyperpigmentation. Ultraviolet light alters pigment production by increasing melanin production, melanin distribution, and melanosome uptake.[8] Ultraviolet light can also increase the formation of free oxygen radicals which alter DNA function and induce inflammation. These factors can exacerbate existing pigmentation such as melasma, inflammation-associated hyperpigmentation, and lentigines.[9] Visible light can also induce the formation of free radicals leading to skin damage and melanogenesis.[9] This response is exaggerated in Fitzpatrick skin types IV to VI.[10] As sunscreens have evolved, chemical sunscreens and sunscreens with inorganic filters continue to play a synergistic role in the treatment of facial pigmentary disorders. Adequate sunscreen use can reduce the effects of ultraviolet and visible light by reducing the melanocyte response to light, thereby reducing pigment production. In addition to having sun protective factors of 30 or greater, broad-spectrum coverage is of utmost importance when addressing facial pigmentary disorders. Non-micronized inorganic filters such as titanium dioxide and zinc oxide or tinted sunscreens containing a combination of iron oxide with inorganic filters can reduce the effects of both ultraviolet and visible light.[9,11] Although the skin has natural antioxidants to protect itself from environmental stimuli, the use of antioxidant-enriched sunscreen formulations may further neutralize the effects of free radicals and reactive oxygen species and enhance the skin's innate protective system.[10,12]

The use of ultraviolet protective clothing is a rising practice in the management of facial pigmentary disorders. Wide-brimmed hats, masks, and head scarves with fabrics that have an ultraviolet protective factor of 40 or greater are useful tools for photoprotection, especially during outdoor activities where reapplication of sunscreen is not feasible.[13] Combining sun protection with other topical therapies can mitigate setbacks and hasten the process of improving abnormal facial pigmentation.

ORAL ANTIOXIDANTS

Similar to antioxidant-enriched sunscreens, oral antioxidants also play a role in the treatment of facial pigmentary disorders. Polypodium leucotomos is a tropical fern extract native to Central and South America. When ingested orally, this extract protects from ultraviolet radiation by eliminating free oxygen radicals and reactive oxygen species.[14-16] Oral Polypodium leucotomos supplements are an adjunct to sunscreens and topical therapies in the management of facial pigmentary disorders including melasma and lentigines. One study concluded that oral supplementation with Polypodium leucotomos extract, in combination with sun protection measures and hydroquinone, led to a statistically significant improvement in melasma severity and quality of life as compared to a hydroquinone and sunscreen only group.[17] A similar finding was observed in a study comparing the efficacy of Polypodium leucotomos extract and sunscreen versus sunscreen only in a Hispanic population. In comparing the melanin index between the groups, the oral Polypodium leucotomos extract group had a 28.8% improvement compared to a 13.8% improvement in the sunscreen only group. These findings support that sunscreen can improve the appearance of melasma and that oral Polypodium leucotomos may serve as an effective adjunct in preventing ultraviolet light-induced exacerbations of Melasma.[18]

OVER-THE-COUNTER PRODUCTS

Over the counter (OTC) skin care products are considered cosmetics and not regulated by the FDA. Strong evidence supporting use in pigmentary disorders as well as safety data are limited. However, various ingredients have been marketed for the improvement of pigmentation including vitamin C, kojic acid, arbutin, licorice extract, niacinamide, cysteamine, and thiamidol. Vitamin C is a potent antioxidant that inhibits melanogenesis via interaction with copper ions at the tyrosinase active site. Ascorbic acid is the most active and potent form of vitamin C. However, it is hydrophilic and easily oxidized. Therefore, other formulations such as ascorbyl-6-palmitate, magnesium ascorbyl phosphate, and tetrahexyldecyl ascorbate are also used in skincare.[19]

Kojic Acid is derived from various species of fungi, such as Aspergillus and Penicillium. It is a well-known, potent competitive inhibitor of tyrosinase. Like ascorbic acid, kojic acid also interferes with copper ions leading to decreased melanin production. Arbutin is a natural compound extracted from the leaves of the bearberry plant. Composed of hydroquinone and D-glucose, arbutin is structurally similar to L-tyrosine and binds to the active site of tyrosinase, inhibiting melanogenesis.[20] Licorice root extract, Glycyrrhia Glabra Linnera, inhibits melanin synthesis and increases the dispersion of melanin.[21] Niacinamide is believed to reduce pigmentation through inhibition of melanosome transfer from melanocytes to keratinocytes.[22]

L-CYSTEAMINE

L-Cysteamine is a biological antioxidant produced by the metabolization of cysteine, a sulfur-containing amino acid.[23] Cysteamine provides double enzyme inhibition of tyrosinase and peroxidase. It also removes dopaquinone from the pathway contributing to its potent depigmenting effects.[24] A randomized double-blinded study of cysteamine versus modified Kligman's formula revealed a 9% greater reduc-

tion in mMASI score in patients treated with 5% cysteamine at 2 and 4 months, (P = 0.005 and 0.001 respectively).[25] Cysteamine is now also available in a 7.5% concentration.

THIAMIDOL

Thiamidol (isobutylamido thiazolyl resorcinol) is a novel human tyrosinase inhibitor that reversibly inhibits melanin synthesis.[26] In vitro, thiamidol was superior to arbutin, kojic acid, and hydroquinone. In the treatment of melasma, thiamidol 0.2% was shown to be superior to hydroquinone 2%.[27] A split-face, double-blind, randomized, controlled trial of participants with mild-to-moderate facial hyperpigmentation was conducted to compare the results of a thiamidol-containing serum and sunscreen versus a thiamidol-containing sunscreen alone. Both groups exhibited statistically significant improvement from baseline, with the group receiving the thiamidol-containing serum and sunscreen experiencing greater improvement.[28]

HYDROQUINONE

Hydroquinone has long been the gold standard of treatment for unwanted pigmentation. Its chemical composition of benzene and para hydroxides allows it to serve as a competitive inhibitor of the tyrosinase enzyme during melanogenesis.[29] Within melanocytes, it prevents the conversion of tyrosine to dopamine, a key step in melanin formation. While research has strongly supported the efficacy of hydroquinone in treating hyperpigmentation, there has also been increasing apprehension about its possible long-term side effects. Hydroquinone is cytotoxic to melanocytes at higher doses.30 Exogenous ochronosis has developed following the long-term topical use of highly concentrated hydroquinone products. Other side effects are contact dermatitis, leukoderma, and hypopigmentation to surrounding normal skin.[29,31] In 2020, the FDA proposed a ban on the sale of over-the-counter hydroquinone. HQ is available as a standard prescription at a concentration of 4%. However, higher concentrations of 6% and 8% are gaining popularity. These prescriptions can be obtained through compounding pharmacies or through online (teledermatology) platforms marketing directly to patients.

TOPICAL RETINOIDS

Topical retinoids are structural and functional analogs of vitamin A that induce the dispersion of pigment granules found inside keratinocytes allowing it to accelerate the turnover of epidermal cells. This allows for the elimination of epidermal pigment.[32] Side effects of tretinoin include itching, burning, excessive dryness, and erythema.[33] In a pooled analysis of a phase 3, double-blind trial of a novel 0.045% tazarotene-containing lotion, Black and Hispanic participants saw a decreased incidence of hyperpigmentation with tazarotene compared to vehicle from baseline to week 12.[34] Retinoids are often used in combination with hydroquinone to enhance efficacy. A 12-week open-label study of preparation containing microencapsulated HQ 4%, retinol 0.15%, and antioxidants on 21 patients (Fitzpatrick IV-VI) with IAH and melasma found that the combined therapy significantly reduced lesion size, darkness, and disease severity starting at week 4 of treatment.[35]

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AZELAIC ACID

Azelaic acid is a naturally occurring C9-dicarboxylic acid known to be a byproduct of pityrosporum fungal mycelia metabolism.[36] Through the inhibition of tyrosine, it has antibacterial and anti-inflammatory properties that improve conditions such as melasma and acne.[37] Its antibacterial effects work by inhibiting cutaneous aerobic and anaerobic organisms such as *P. acnes.* This, along with its selective cytotoxic effects on hyperactive melanocytes, improves hyperpigmentation while having minimal effects on normally pigmented skin.[38] Azelaic acid also inhibits free radical production with neutrophils, making it especially effective in treating IAH.37 Over-the-counter concentrations have not been well studied. A systematic review of 20% azelaic acid versus 4% hydroquinone in the treatment of melasma found that treatment with azelaic acid yielded a lower mean change in melasma area severity index (MASI) than hydroquinone treatment. However, there was no difference observed between treatments using an objective response scale.[39] Azelaic Acid is currently available as a prescription at 15% and over the counter in concentrations up to 12%.

TRANEXAMIC ACID

Tranexamic Acid (TXA) is a synthetic derivative of lysine that inhibits plasminogen by reversibly blocking the lysine-binding sites on plasminogen. Blocking UV-induced plasmin activity in keratinocytes decreases prostaglandin production and consequently, melanocyte stimulation.[40] Tranexamic acid is used off-label in the treatment of melasma and other pigmentary disorders. For melasma, reported oral doses

range between 500 and 1500mg daily. However, no consensus has been reached on dose or duration.[41] Common side effects of oral tranexamic acid are nausea, abdominal pain, and heartburn.[42] The most feared complication is thrombosis. Tranexamic acid is contraindicated in patients with a known allergy to TXA, impaired color vision, renal disease, malignancy, anticoagulant therapy, intracranial bleeding, a history of thromboembolism, or active thromboembolic disease. Caution is advised for patients who smoke or who are on procoagulants such as oral contraceptives or hormone replacement therapy.[40]

PEELS

Chemical peels are well-documented, effective treatments for disorders of hyperpigmentation. The general mechanism of action involves the removal of unwanted melanin in the epidermis and/or dermis, depending on the strength of the peel. However, these agents should be used with caution as they can irritate the skin and lead to burns, IAH, and scarring, especially in patients with skin of color.[43] Very superficial and superficial peels treat the epidermis. Commonly used peels include trichloroacetic acid 10-30%, glycolic acid 30-70%, salicylic acid 20-30%, and Jessner's solution- composed of salicylic acid, lactic acid, resorcinol, and ethanol.[44] A comparative study of 35% glycolic acid vs 20% salicylic-10% mandelic acid vs. phytic acid peels in the treatment of acne and post-acne hyperpigmentation showed improvement in all groups following biweekly peels for a total of six sessions ($P = 0.034$).[45]

Medium-depth peels treat the epidermis to the upper reticular dermis and should be used with extreme caution in patients with darker skin types. Medium-depth peels include monotherapy with trichloroacetic acid 35-50%, as well as combination or layered peels such as trichloroacetic acid 35% with glycolic 70%, and Jessner's solution with trichloroacetic acid 35%.[44] It is important to recognize the clinical signs that signal depth of peeling. White frost with a pink or erythematous base generally corresponds to a full-thickness epidermal peel to the papillary dermis, while a solid white frost indicates peeling down to the reticular dermis.[46] Given the potential for complications including scarring and infection with medium-depth peels, skin preparation, method of application, number of layers, contact time, and prophylaxis should be predetermined.

LASERS AND LIGHT-BASED THERAPIES

Lasers and light-based therapies are effective treatment modalities for the treatment of hyperpigmentation, especially in cases that may be unresponsive to the therapies described above. For pigmented lesions, the laser energy is preferentially absorbed by the target chromophore, melanin. Appropriate selection of wavelength and parameters including pulse duration and fluence are required to achieve efficacy and maintain safety. The selective window for targeting melanin lies in a wavelength between 630nm and 1100 nm.[47]

Many lasers and light-based devices have been studied in the treatment of hyperpigmentation such as picosecond lasers, Nd:YAG lasers, and intense pulsed light. Studies have shown picosecond lasers to be highly effective in the treatment of disorders such as IAH and melasma with improvement after several sessions.[48] The 1064 nm Q-switched Nd:YAG laser has also been widely studied for the treatment of hyperpigmentation, specifically in melasma. The 1064 nm Q-switched Nd:YAG laser is very effective in the treatment of hyperpigmentation with a safer side effect profile when compared to other laser devices.[49] Intense pulsed light (IPL) is a non-laser light source that emits light with wavelengths between 515 nm and 1200 nm. Wang et al performed a randomized control trial in patients with melasma comparing IPL plus hydroquinone to hydroquinone alone.[50] Patients in the IPL treatment group obtained a higher percentage of clearance compared to hydroquinone monotherapy (39.8% clearance vs. 11.6% clearance).[50] For sustained and significant results, several sessions are recommended. Side effects of lasers and light devices include erythema, edema, pruritus, scaling, blisters, and bruising. For melasma, laser and light therapies have generally been reserved for refractory cases as the heat generated from the devices may potentially exacerbate the hyperpigmentation. It is important to note that because melanin is the target chromophore, patients with skin of color are at an increased risk of complications such as hypopigmentation or hyperpigmentation. Therefore, the use of test spots and/or pretreatment with hydroquinone may be useful, especially in patients with skin of color.

MICRONEEDLING

Microneedling is a popular technique for skin rejuvenation whereby repetitive micro penetration leads to skin remodeling and transcutaneous elimination of pigment.[51] Microneedling performed in-office is well tolerated in all skin types with a low complication rate. However, devices marketed for at-home use should be discouraged out of concern for excessive epidermal trauma and sterility. The efficacy of microneedling in melasma has been demonstrated in various studies using both handheld rollers and motorized devices.[51] Microneedling also serves to enhance dermal drug delivery of depigmenting agents such as tranexamic acid. Kaur et al reported statistically significant improvement in a randomized, split-face study comparing microneedling followed by the application of 10% TXA to microneedling alone.[52] TXA

can also be administered via transdermal injection. A split-face study comparing intradermal injection of TXA versus TXA with microneedling for melasma revealed significant improvement in both groups, with no significant difference seen between both treated sides ($P < 0.001$).[53] Although, the authors note that patient satisfaction was higher on the microneedling-treated side.

Pigmentary disorders remain a leading concern for individuals seeking dermatologic care. Due to the growing number of topical, oral, and procedural interventions, it is important to be familiar with various mechanisms of action to maximize efficacy and safety, leading to better patient satisfaction. ■

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