Melasma, a commonly acquired hypermelanosis, presents as symmetrical irregular to dark-brown macules on sun-exposed areas such as the face, particularly over the forehead and malar areas, and extrafacial sites such as the neck and forearms and is undoubtedly one of the top five dermatological referrals we see in everyday practice. Majority of the literature in melasma studies the condition in women, but occurrence in men is not uncommon. A few studies on melasma in men have been conducted, and they report the occurrence as high as 10% in Puerto Rico and 25.8% in India. Being a disorder of hyperpigmentation present on exposed areas such as the face, it can be a source of embarrassment for the patients including the men, resulting in a negative impact on the quality of life.

The major etiological factors include genetic susceptibility, exposure to ultraviolet (UV) radiation, and sex hormones. Melasma, as we have all seen in our experience, is an extremely difficult condition to treat and notorious for relapse and recurrence. In our quest for treatment, we began with limited but powerful drugs, which include hydroquinone (HQ) and the modified Kligman’s regimen combination creams which inhibit melanogenesis by inhibiting the rate-limiting enzyme tyrosinase. The reduction of pigmentation imparts excellent clinical efficacy to these drugs and makes them the gold standard, even today. However, inconsistent/ incomplete results and considerable adverse effects, both on short- and long-term use, make it extremely important to look for alternative drugs which provide similar results but lesser side effects.

The journey toward demystifying this path begins with solving the enigmatic puzzle, the mammoth task of deciphering the pathogenesis of melasma, and the understanding of which has undergone a paradigm shift over the years. In 1981, Sanchez et al., using clinical and histological characteristics, classically described melasma as a linear model and classified on the basis of localization of melanosomes in the skin, as epidermal, dermal, and mixed. Moreover, in our practice, we conform to the notion that epidermal melasma responds well to the topical depigmenting agents, while the other two variants are much more challenging to treat. However, with the use of newer investigational modalities such as in vivo reflectance confocal microscopy, immunohistochemistry, and electron microscopy, it has been discovered that the distribution of melanin and melanophages is heterogeneous and perhaps suggests that all melasma is in fact “mixed.”

Further, involvement of the dermis has been demonstrated which includes findings such as increased solar elastosis and vascularity in dermis of melasma patients. We have now begun to acknowledge that melasma, rather than being a rigid linear epidermal problem, is in fact a complex interplay among the epidermal melanocytes, keratinocytes, dermal fibroblasts, and vascular endothelial cells. The elaboration of this newer concept of pathogenesis has identified several other potential targets for research and treatment in the field of melasma.

Recently, studies have suggested that interactions between altered cutaneous vasculature and melanocytes may influence the development of hyperpigmentation in the overlying epidermis. Vascular endothelial growth factor (VEGF) could have a direct influence on melanogenesis through its receptor on melanocytes as well as on vascular endothelial cells, which on exposure to UV radiation may release cytokines and soluble factors such as plasminogen, which might be a possible cause of hyperpigmentation in melasma.

These findings led to the use of plasmin inhibitor tranexamic acid in melasma, in both oral and topical forms. Although some studies have found it to be effective, the results have been mostly inconsistent, temporary, and short lived. Further, the vascular theory does not explain the inconsistent results of copper bromide or pulsed dye laser in melasma, which are hypothesized to reduce the VEGF-induced angiogenesis and thus the hyperpigmentation. Further research needs to be done to generate more clinical evidence to put these drugs and physical modalities to larger clinical use.

Among the other causal factors of melasma, role of inflammation is garnering much interest. Majority of the inflammation in melasma in the epidermis is known to be induced by UV radiation. UV induces melanogenesis by its direct effect on DNA and melanocyte membranes that release diacylglycerol and arachidonic acid, which have a putative role in melanogenesis. Further, UV light induces an increase in cell surface expression of receptors for keratinocyte-derived paracrine melanogenic factors such as basic fibroblast growth factor, nerve growth factor, endothelin-1, and the proopiomelanocortin-derived peptides such as melanocyte-stimulating hormone, adrenocorticotrophic hormone, and beta-endorphin. Keratinocytes also secrete nitric oxide in response to UV radiation. These inflammatory mediators are
overexpressed in lesional skin of melasma patients and induce local increase of vessels and inflammatory cells, all of which contribute to the hyperpigmentation in melasma.\(^9\) This has opened the doors to research on potential efficacy on anti-inflammatory molecules. Various anti-inflammatory agents such as liquorice extract, orchid extract, and mulberry extract are used topically, while oral preparations of proanthocyanidin, pycnogenol, oral Polypodium leucotomos extract, and Vitamin C have been found to find a foothold as potential treatments for melasma. Most of these have been studied largely in vitro with fewer in vivo studies. Although the results are encouraging, further studies need to find evidence of the laboratory results converting to clinical benefits. Another antioxidant molecule glutathione, both oral and injectable, has been the talk of the town due to its potential of reducing pigmentation and making the skin shade fairer by a shade or two. Much has been said about its role in melasma, but it is yet to be backed by even a single study in the same. It shall have to wait for more data on its efficacy on long-term safety.

While most of the studies have focused on reducing melanogenesis by inhibiting tyrosinase, the concept of hyperactive melanocytes has begun to take a footing. In melasma, the lesional melanocytes are found to be more biologically active than those in normal skin, and there is an upregulation of genes involved in melanogenesis-tyrosinase, TYRP1, TYRP2, and MITF in melasma lesions.\(^9\) These findings suggest that inhibiting the activity of melanocytes rather than only melanin synthesis would be more effective. Many new agents such as aloesin, arbutin, ellagic acid, and antisense oligonucleotides have been found to act on these targets. The in vivo and in vitro studies give favorable efficacy and safety outcomes and in some studies better than the conventional agents such as HQ. This is an upcoming concept, but it needs to be backed by more literature for it to be put to widespread use.

Moving on from the medical management of melasma, the other therapeutic modalities include chemical peels and laser and light treatments, which are particularly beneficial for patients less responsive/refractory to topical therapy. Chemical peels have largely established their role in the treatment of hypermelanoses such as melasma, but the potential side effects of irritation and postinflammatory hyperpigmentation (PIH), especially in the dark-skinned individuals, sensitize us to exercise caution while using these in melasma patients.

A multitude of laser and light devices have been used in melasma with varying degree of success. The vast arrays of machines with multiple protocols that are different among most studies give us a fair idea that no single modality is uniformly effective. It is also difficult to decipher the results of studies involving lasers as most of them have small study groups, short trial period with limited follow-up. There are multiple reasons for the same like multiple chromophores present in the skin, the variable depth of melanin and melanophages in the skin combined with the act that lasers only accelerate the pathways for removal of melanin and melanophages but do not target the melanin production itself. Furthermore, they present a risk for PIH or a rebound melasma flare, especially the dark-skinned patients.

Hence, the treatment of melasma should focus on underlying etiological factors, namely, addressing endocrinal abnormalities, cessation of suspected drug, and photoprotection with special emphasis on visible and infrared light. Sunscreens containing inorganic constituents, such as iron oxide, would definitely help treatment. Time-tested topical HQ and non-HQ therapies still remain the first line of treatment for melasma with adjuvants such as chemical peels and lasers being reserved as second line and third line of treatment, respectively. A group of Indian Pigmentary Experts from Pigmentary Disorders Society have attempted to review and give practical tips in management of melasma, elsewhere in this special issue. The quest for a perfect competitor for topical HQ still continues. There is an increasing excitement and hope associated with the newer oral agents, but we need to be cautious regarding their side effects and long-term prevention in recalcitrance of melasma. Combination therapies and lifelong maintenance of treatment are the way forward for treating melasma. The articles in this invited symposium on melasma discuss available evidence and brings forward a suggested treatment algorithm by experts from Pigmentary Disorders Society (PDS) in a collaborative discussion called South Asian Pigmentary Forum (SFP).

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