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REVIEW ARTICLE

An Updated Insight about Interventional Treatment of Melasma

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ABSTRACT

Background*:* Melasma is a highly prevalent hyperpigmentation problem that affects a large percentage of the global population. It is most seen in women and those with Fitzpatrick Skin Types III–VI. This hyperpigmentation condition has a complicated and multi-factorial pathophysiology. Intense exposure to ultraviolet radiation, hormonal impacts, and hereditary susceptibility are the main contributors to the development of this illness. Melasma is classified as either epidermal or dermal, depending on the pattern of its pigmentation. Diagnosis of melasma is typically by clinical examination. Melasma Area and Severity Index (MASI) and modified MASI (mMASI) continue to be the most reliable melasma scoring methods. Melasma is difficult to treat because recurrences are common, and most patients do not have full lesion clearance. **Conclusions***:*Current treatment of melasma includes the use of a combination of photo protectants, skin lighteners (both oral and topical), and resurfacing techniques. Interventional therapies for melasma, both established and novel, are discussed in this article.
Keywords: Melasma; Microneedling; Chemical peeling.

INTRODUCTION

In adults, particularly reproductive-aged women, melasma manifests as photo-exposed patches of hyper melanosis that worsen over time. Skin pigmentation caused by sun exposure or inflammation typically resolveswhen the inducing stimulus stops, but melasma is an exception. Hyper functional melanocytes, which are responsible for producing and transferring mature melanosomes to the entire epidermis, are an evolving consequence of changes in many skin layers and cell types that cause melasma [1]. One of the most prevalent dermatological concerns that dermatologists around the globe encounter is melasma [2].

Aetiology and Pathogenesis:

Both internal and external factors contribute to the complicated pathophysiology of melasma. To treat this skin problem correctly, it is highly important to understand the suspected aetiology and pathophysiology [2].

I-Genetic Factor:

Melasma is more common in some ethnic groups than others. Melasma risk factors might include a family history of the condition [3].When considering epidemiological risk factors, facial melasma primarily follows an inherited pattern. In those who are genetically predisposed, environmental factors can trigger the development of the disease [4]. Despite the lack of genome-wide studies examining these genes, recent studies have shown that linked regulatory proteins play a role in pigmentation, energy metabolism, response to oxidative stress, and other processes. It is, therefore, believed that melasma's

pathophysiology may be significantly impacted by the aberrant expression of these genes [5].

II- Ultraviolet and visible light exposure:

While keratinocytes, mast cells (MC), and fibroblasts regulate melanogenesis via paracrine pathways, ultraviolet radiation (UVR) directly increases melanogenesis in melanocytes. However, radiation of different wavelengths evokes distinct effects on the skin [6].

The basement membrane (BM) and the epidermis are the primary targets of ultraviolet B radiation, whereas the upper dermis is the domain of ultraviolet A. The continuous melanogenesis seen in melasma is a result of photoaging, oxidative stress, and inflammation brought on by long-term exposure to ultraviolet radiation [7]. It also causes keratinocytes to produce p53, which then triggers the production of propiomelanocortins and laminin-332, which promote melanogenesis. Proopiomelanocortinincludes adrenocorticotropic hormone (ACTH), melanocyte-stimulating factor (MSH), and β-endorphin [8].

III- Hormonal Factor:

The most common causes of melasma, including hormone replacement treatment, oral contraceptives, and pregnancy, suggest that hormones have a significant impact on the development of the condition [9]. Melasma develops in 8–34% of women who take oral contraceptives or undergo hormone replacement therapy. Changing from a combination oral contraceptive to a hormone-releasing intrauterine device resulted in spontaneous improvements in melasma patients, according to recent research [10].

IV- Communication between melanocytes and other cells:

The melanocytes aren't the only ones responsible for melasma. Melasma actually develops as a result of a complex web of interconnected biological processes that includes fibroblasts, keratinocytes, mast cells, and endothelial cells, as well as the dermal vasculature [7].Electron microscopy revealed an increase in mature melanosomes in keratinocytes and melanocytes, as well as an increase in cytoplasmic organelles in melasma lesions. Cell types such as melanocytes, keratinocytes, and fibroblasts all contribute to the production of autocrine and paracrine substances that control melanocyte activity. Paracrine connections between skin cells, such as keratinocytes, fibroblasts, and melanocytes, are crucial for controlling sun-induced epidermal pigmentation [11].

V- Dermal and Vascular components:

The basement membrane zone plays a significant role in regulating the skin's surface tension and elasticity. Dermal examinations of melasma patients revealed elevated melanin levels and an abundance of pigmented basal cells, suggesting that basement membrane disruption plays a role in the development of this skin condition. Melasma lesions showed structural damage to the basement membrane zone, which manifested as holes, ruptures, a loss of lamina lucida anchoring fibres, and a lessening of lamina densa density [12]. Immunohistochemistry further showed that dermal blood vessel size and number were significantly elevated in melasma lesional skin. Some have even postulated a positive correlation between the amount of

pigmentation and the number of vessels. It is believed that deoxyhaemoglobin has a major role in skin tone [13] Reflectance confocal microscopy (RCM) and dermoscopy both revealed that melasma has more blood vessels than normal. Melasma lesions also displayed elevated levels of vascular endothelial growth factor (VEGF) [13].

Diagnosis of melasma:

Melasma is typically diagnosed by clinical examination because of its distinct look. In addition to the distribution pattern, which is the primary criterion for clinical classification, the depth of melanin pigment divides melasma into four distinct forms [14]. To further refine the process of melasma subtyping, additional imaging modalities such as reflectance confocal microscopy, dermoscopy, and Wood's lamp can be utilised. Therapeutic outcome prediction and prognosis are both aided by these categorisations[15].

Wood's Lamp:

Most people use Wood's lamp to categorise melasma since it shows how the affected skin's pigmentation differs into four subtypes: epidermal, dermal, mixed, and indeterminate [16].If pigmented areas are brighter when seen through a Wood's lamp, it means that the epidermis (the outer layer of the skin) has a higher concentration of melanin than the dermis (the deeper layer of the skin) (dermal subtype). When melasma pigmentation includes both enhancing and non-enhancing regions, it is likely a mixed variant [15].

Dermoscopy:

Clinical trials have demonstrated that dermoscopy is an effective tool for evaluating melasma because it allows for the objective classification of skin pigmentation, the visualisation of the vascular component, and the monitoring of therapy response [17]. Melasma is classified as either epidermal or dermal, depending on the pattern of its pigmentation. A uniform brownish-grey pigmentation characterises epidermal melasma, whereas an irregular and mixed network of pigmentations characterises dermal melasma. Finally, melasma is a mixed subtype since both characteristics often occur together [18]. Dermoscopy also reveals a vascular component, which is found in many melasma patients, according to recent studies [19].

Reflectance Confocal Microscopy:

Reflectance, which is a new non-invasive imaging method called confocal microscopy, has just been developed. It can examine the skin in real-time up to the papillary dermis level and provides cellular resolution like histology. A confocal microscope concentrates a diode laser's near-infrared light (830 nm) on a tiny skin target. The light is reflected, collected, and recomposed into a two-dimensional greyscale image by computer software as it passes through various cellular structures with varied refraction indices. These structures are mostly assembled of keratin, melanin, haemoglobin, and cellular organelles [19]. Melasma Area and Severity Index (MASI) and modified MASI (mMASI) continue to be the most reliable melasma scoring methods, and they should be utilised consistently in all melasma therapy trials. There is a lot of hope in the automated mMASI (aMASI) method that uses computer image analysis, but it needs to be tested for consistency and global application [20].

Treatment:

Melasma is difficult to treat because recurrences are common, and most patients do not have full lesion clearance. Daily sun protection is the initial line of defence, with topical bleaching treatments utilised for milder cases. Oral treatment is an option for more severe and/or resistant cases. Procedures represent an important adjunct to the treatment of melasma. Microneedling, chemical peels, lasers and light-based technologies are frequently added to the melasma treatment protocol. Individuals can get faster results with a mix of oral drugs and procedures with topical bleaching chemicals. However, there is a lack of research on measures that can effectively prevent future relapses [21].

Sun Protection:

Direct sun exposure, along with pregnancy, is a major risk factor for melasma; in as many as 84% of cases, sun exposure was the actual cause of melasma, and in as many as 51% of cases, it was the trigger. Sun exposure, whether from work or pleasure, is often stated by patients with melasma [22].

Patients with melasma should know that they still need to wear sunscreen near windshields since UVB, UVA, and short-wavelength visible light (VL) can trigger melanogenesis in melasma. Even in partially shaded areas or close to windows, a significant quantity of radiation can reach the skin since UVA and VL can penetrate windshields and window glass [23]. When it comes to pigmentary disorders, topical sunscreens are an important behavioural strategy for sun avoidance, especially for melasma treatment [24].

Topical treatment for melasma:

There is a plethora of topical medications that can be used to treat melasma. Because of its exceptional effectiveness, hydroquinone is regarded as the gold standard. Niacinamide, retinoids, steroids, tranexamic acid, azelaic acid, glycolic acid, salicylic acid, ascorbic acid, and kojic acid are some other topical agents. Many people consider triple combination therapy, which includes hydroquinone, a retinoid, and steroids, as the first line of defence against melasma because of its proven effectiveness in clinical trials. Sunscreen is also crucial for the effectiveness of any treatment plan [25].

Oral treatment for melasma:

One option for oral administration is tranexamic acid (TA), a fibrinolytic drug that inhibits the conversion of plasminogen to plasmin and, by extension, the binding of plasminogen to keratinocytes. TA is a synthetic derivative of lysine. Reducing prostaglandin and fibroblast growth factor synthesis and arachidonic acid release are examples of downstream effects. Two substances that promote the production of melanin include prostaglandins and fibroblast growth factor. Both mast cells and angiogenesis are reduced by TA [26]. To effectively treat melasma, dermatologists need a thorough understanding of the melanogenesis pathway. This knowledge helps them choose the topical therapy modalities and adjuvant medications that will work best for their patients. The primary ways in which different topical agents work include, but are not limited to, blocking tyrosinase activity, decreasing melanocyte activity, and interfering with melanosome transfer, among other things [27].

Interventional Treatment for Melasma:

An integral aspect of the multimodal strategy for melasma is the use of one or more of the following interventional procedures:

I- Chemical Peelings:

Chemical peels accelerate the epidermal keratinocyte turnover rate. The inflammatory process, which produces cytokines, causes dermal remodelling, epidermal remodelling, and the removal of melanin at this accelerated rate. These substances enhance the production of collagen and elastin by fibroblasts. Melasma treatments would benefit from this since theyreduce sun-induced solar elastosis and ageing fibroblasts (senescent fibroblasts). Sunlight, specifically UVA and UVB rays, can promote senescent fibroblasts by increasing their secretion of melanogenic cytokines. In addition, senile lentigo and other age-related pigmentary diseases may involve senescent fibroblasts [28]. There are three different depths of chemical peeling, named after the skin layers and histological levels reached: superficial, medium, and deep. It is worth mentioning that darker-skinned persons are more suited to superficial peels performed in series rather than deeper peels [29] Topical treatments for melasma often involve chemical peeling in addition to hydroquinone, an antioxidant phenolic chemical that inhibits tyrosinase, a process involved in melanogenesis. Add a broad-spectrum sunscreen for added protection. To achieve even better outcomes, further treatments like microneedling could be incorporated [30]. For further pain relief, try using an ice pack massage for 20 minutes or turning on a cool fan. Although side effects are uncommon, dark-skinned people should be worried about the possibility of hyperpigmentation. To prevent post-inflammatory hyperpigmentation, which can be caused by irritation, it is crucial to avoid sunlight until the skin has healed. Additionally, refrain from applying makeup or cosmetics after the procedure [30].

II- Microneedling:

The initial applications of microneedling were for the treatment of skin laxity and acne scars. Despite this, these individuals had decreased melasma and post-inflammatory hyperpigmentation. Early recovery of melasma was observed after a significant skin injury was caused by fine microneedling using a roller. The damage manifested as diffuse erythema with some bleeding sites [31]. There is still some mystery about how microneedling works to improve melasma. Theoretically, melanin transcutaneous removal is boosted after microneedling due to early keratinocyte growth. Furthermore, microneedling helps repair damaged basal membranes and improves solar elastosis and pendulum melanocytes, two signs of photoaging in the skin [32]. In addition, microneedling is employed to increase the trans epidermal penetration of topical bleaching agents, which is a way of drug administration. Nevertheless, not everyone agrees on the optimal penetration endpoint. The product's bleaching effect is likely to be dependent on how often you apply it and how deeply it penetrates the skin [32]. Dark skin can safely undergo fine microneedling [32]. Despite claims that radiofrequency microneedling (Microneedle RF) can effectively cure refractory melasma, no large-scale randomised controlled trials have been conducted [33]. By delivering energy to the dermo-epidermal junction and dermis with minimal injury to the epidermis, radiofrequency microneedling improves the

impaired extracellular matrix (ECM), which is commonly found in melasma lesions, and the trans epidermal elimination of melanin and drug delivery. This increases the safety profile and decreases the downtime post-procedure, in contrast to other ablative laser modalities [33]. In a split face study, fractional microneedle RF was combined with low-fluence 1,064 nm quality switched (QS) ND YAG laser versus low-fluence 1064 nm QS ND YAG alone. Combination treatment showed earlier and better response at the end of 5 treatment sessions two weeks apart. The fractional microneedle RF session was performed on the same day following the QS session with a single pass of 50% intensity, 1 mm depth, and 50 ms pulse duration 50 using minimally invasive 5×5 parallel rows of non-insulated bipolar electrodes [33]. Possible side effects of the surgery include minor redness and swelling (oedema). Within a day, you shouldn't feel these negative effects anymore. Rarely people of colour may experience burns due to the high temperatures produced by radio frequency treatments [33].

III- Platelet-Rich Plasma and Intradermotherapy:

The stratum corneum is hydrophobic, making it difficult for water-soluble compounds to penetrate. This poses a major obstacle to melasma treatments. A higher drug concentration in the target area with fewer amounts is achieved by intradermotherapy, which involves the direct delivery of drugs into the dermis. The result is a stronger and longer-lasting effect with minimal side effects. Substances should be dissolved in sterile water before intradermal injection; mixes should not be used. It is recommended to use separate syringes for injecting different substances [34]. A substantial decrease in mMASI score was shown in clinical trials comparing pre- and post-treatment for PRP therapy, whether administered alone or in conjunction with other combinations such as microneedling. Both patients and doctors were quite satisfied with the results of the PRP for melasma effectiveness study. Patient satisfaction was also better with PRP with microneedling compared to PRP administered intradermally [35].

IV- Laser and Light Technologies:

The target of laser treatment for melasma is the pigment cell (melanocytes). While it may seem straightforward to target melanocytes of melasma with a laser, it is much more complex than that. Other cells and skin structures are involved in the excess melanin synthesis in melasma pathogenesis, and these should be targeted as well. Thus, laser monotherapy is not associated with significant improvement in melasma. Other topical and physical therapies and even oral treatments might be needed to reach satisfactory improvement [36]. In clinical practice, the Q-switched Nd-YAG is the most used laser in treating melasma, particularly in toning mode. Toning mode photo thermolysis involves subcellular selective absorption of light with pulse lengths of nano- or picoseconds and extremely low fluences administered in successive treatment sessions via several passes. With somewhat lengthy delay intervals, this method has demonstrated considerable success [37, 38]. Micek and co-workers irradiated the entire face twice with the following parameters: (pulse duration, 5 ns), 6–8mm in diameter, with an energy density of 1.7–3.5 J/cm 2.5Hz. Then, another 4–8 passes were directed to the melasma site.

Treatments were repeated at one to two weeks intervals. All the factors above were adjustable in response to the patient's level of discomfort, skin redness, and oedema [37].

Despite the satisfactory results, there wasan increased frequency of dyspigmentation either in the form of post-inflammatory hyperpigmentation (PIH) or confetti‐like hypopigmented macules. There were also reports of melasma recurrence. Such complications are more commonly encountered at higher fluences [38]. Other reported side effects included pain during the procedure. Hence, pre-operative topical anaesthesia was used. Post-operatively hydrocortisone and strict photoprotection protocol might decrease such adverse effects [37]. Lasers that target water, in addition to pigment-targeting lasers, are another option for treating melasma lesions. Lasers that use relative fractions (CO2 and Er: YAG) [39] Ten women with unresponsive Fitzpatrick skin types III–V were the subjects of a clinical trial by Cameron and colleagues. Using 1535 and 1550 nm wavelengths, 6–12 mJ per microthermal zone, 2000–3500 mHtz/cm2, and 1–2-week intervals, they experimented. The patient underwent four or six sessions of treatment. Sixty percent of patients saw a complete or near-complete resolution, whereas thirty percent saw a partial or no improvement. Post inflammatory hyperpigmentation was observed in a single subject. Though ablative lasers can cause dyschromia due to their strong thermal effect, fractional resurfacing offers a new treatment method for melasma that combines reduced risk and downtime with substantial efficacy. Therefore, to lessen the impact of this issue, brief pulses with a low energy density are suggested [39]

Below the ablative threshold, non-ablative fractional lasers (NAFL) cause coagulative damage to columns inside the dermis. Throughout the treatment, there are no apparent wounds on the stratum corneum. Redness and swelling are the most typical initial side effects. Curiously, the epidermal barrier is temporarily compromised after treatment, allowing drugs to be delivered [38]. To promote neocollagenesis and remodelling, four different NAFL wavelengths—1440 nm, 1540 nm, 1550 nm, and 1927 nm—are utilised. These wavelengths pass through the epidermis and reach the midreticular dermis, with a maximum depth of about 1500 microns. It is believed that the primary mechanism for melasma improvement is the trans epidermal elimination of these microthermal therapy zones in the post-treatment phase, which helps remove dermal melanophages [38]. The researchers Wanitphakdeedecha and colleagues used a 1927 thallium non-ablative laser with a 100 μm microbeam size, a pulse duration of 1.7 ms, and a fluence of 5 mJ in their study. Melasma lesions were subjected to four more passes of radiation, while the entire face was irradiated twice. The sessions were scheduled to occur once every week [38]

Certain types of light-based treatments are associated with the worsening of melasma lesions, such as intense pulsed light (IPL)andbroadband (BB) light, so they should be avoided in people with melasma [36].

V- Dermabrasion:

It has been suggested that a micromotor and a revolving diamond probe can be used to perform superficial mechanical abrasion on

the skin, which would increase epidermal turnover and eliminate melanocytes in the epidermis, thus improving melasma [40].

In a split-face trial, microdermabrasion was found to be more effective in treating melasma than glycolic acid peel alone (70 percent vs 70 percent). After six sessions of microdermabrasion on one side of the face every two months using 30 cmHg vacuum suction with three passes (horizontal, vertical, and oblique), the entire face was treated with 70% glycolic acid. There was a brief reddening of the skin during microdermabrasion, but it went away after a few minutes. Strict photoprotection measures, including avoiding direct sun exposure and using only the prescribed emollients, were advised to patients. Keep in mind that the epidermis and top dermis can be restored with mild dermabrasion. Nevertheless, temporary darkening following inflammation is likely. Although microdermabrasion with aluminium oxide may improve medication penetration, it has no direct role in treating melasma because it solely impacts the stratum corneum [40]

CONCLUSIONS:

Treatments for melasma that include intervention often use a combination of photo protectants, skin lighteners (both oral and topical), and resurfacing techniques.

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