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Update on Melasma Treatments

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ABSTRACT

Melasma is a prevalent hyperpigmentation condition known for its challenging treatment due to its resemblance to photoaged skin disorders. Numerous studies have shed light on the intricate nature of melasma, which often bears similarity to photoaging disorders. Various therapeutic approaches, encompassing topical and systemic treatments, chemical peeling, and laser therapy, have exhibited efficacy in managing melasma in previous research. However, melasma often reoccurs despite successful treatment, primarily due to its inherent photoaged properties. Given that melasma shares features with photoaging disorders, including disruptions in the basement membrane, solar elastosis, angiogenesis, and mast cell infiltration in the dermal layer, a comprehensive treatment strategy is imperative. Such an approach might involve addressing epidermal hyperpigmentation while concurrently restoring dermal components. In this article, we provide a comprehensive review of conventional treatment methods frequently employed in clinical practice, as well as innovative treatments currently under development for melasma management. Additionally, we offer an extensive overview of the pathogenesis of melasma.

Keywords: Melanosis; Melasma; Pathology; Skin aging; Therapy

INTRODUCTION

Melasma is a common, acquired hyperpigmentation disorder characterized by asymptomatic, irregular-bordered, symmetrically deposited light-to-dark brown macules and patches on the sun-exposed area. It is known to usually affect women in their third or fourth decades with Fitzpatrick skin types III-IV[1,2]. The most cited etiologic factors of melasma are genetic susceptibility, sexual hormone, and ultraviolet (UV) exposure[1-3]. Melasma is often resistant to conventional treatments and often recurs even after successful treatment. To understand the challenges of treating melasma, it is essential to understand its pathophysiology. Several recent studies have updated our understanding of melasma.

PATHOGENESIS OF MELASMA

Previously, melasma was regarded as a melanocyte disorder. However, recent studies have integrated the roles of dermal components such as mast cells, solar elastosis, and neovascularization in melasma pathogenesis alongside melanocytes. When UV radiation accumulates, chronic dermal inflammation occurs, activating fibroblasts[4]. Subsequently, UV irradiated fibroblasts secrete stem cell factor (SCF), which induces melanogenesis by signaling with its receptor, c-kit, located in the epidermis[5]. Additionally, senescent fibroblasts are elevated in the lesional skin of melasma compared to perilesional normal skin. Senescent fibroblasts are believed to produce more skin-aging-related proteins,

such as SCF[6]. Moreover, in the lesional skin of melasma, there is an upregulation of modulators associated with Wnt signaling[7]. Furthermore, there is a reduction in the expression of Wnt inhibitory factor-1 (WIF-1) in the hyperpigmented skin of melasma patients[8]. The downregulation of WIF-1, which can occur in epidermal keratinocytes and dermal fibroblasts, is implicated in the development of melasma due to its role in stimulating melanogenesis and the transfer of melanosomes through the upregulation of both canonical and noncanonical Wnt signaling pathways[8]. Meanwhile, the release of frizzled-related protein 2 (FRP2) serves as a stimulant for melanogenesis through the activation of the β-catenin signaling pathway[9]. Additionally, UV-induced cyclooxygenase-2 (COX-2) is recognized for its ability to stimulate melanocytes further[10].

In the lesional skin of melasma, pendulous melanocytes dropped into the dermis, characteristic of the disease, and dermal melanophages were observed[11]. Dermal melanin content is thought to be promoted by disruption of the basement membrane[4]. Using periodic acid-Schiff-Diastase (D-PAS) staining and anti-collagen type IV immunohistochemistry, 95.5% and 83% of skin samples from melasma patients with Fitzpatrick skin types IV and V showed basement membrane disruption, respectively[12]. Chronic UV exposure activates metalloproteinases2 (MMP2) and MMP9 to degrade type IV and VI collagen in the basement membrane[2]. The decent of melanocytes and melanin in the dermis facilitated by the basement membrane makes melasma refractory to treatments that target epidermal pigmentation.

Mast cells are more frequently observed in melasma-affected skin than in normal skin[13]. UV radiation appears to promote histamine release from dermal mast cells[14]. The role of histamine in melanogenesis is still unclear, but it is thought to be related to growth-differentiation factor-15 (GDF-15), which belongs to the transforming growth factor (TGF-β) superfamily[15]. Also, histamine is known to stimulate human melanocytes through protein kinase A activation via H2 receptors[16]. Furthermore, chronic UV irradiation increases the tryptase released by mast cells[13]. Mast cell-released tryptase facilitates the degradation of type IV collagen by activating latent forms of MMPs or directly damaging extracellular matrix (ECM) components[17]. Consequently, the increased tryptase released by mast cells can induce basal cell disruptions in melasma patients. Moreover, mast cells release diverse angiogenic factors, including basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and TGF-β[18]. Furthermore, prolonged exposure to UV radiation leads to the development of solar elastosis, characterized by the abnormal accumulation of elastic tissue in the dermis, a phenomenon frequently observed in the affected skin of individuals with melasma[2,19]. It is proposed that mast cell-secreted tryptase plays a role in inducing solar elastosis by stimulating fibroblasts to produce elastin[2]. Additionally, granzyme B, which is secreted by mast cells, is known to promote ECM degradation after extended UV exposure[20].

Previous studies have reported a significant increase in the number and size of blood vessels in the affected skin of individuals with melasma[21,22]. Within these altered blood vessels, there is an upregulation of VEGF expression[22]. VEGF is known to trigger the release of arachidonic acid and the phosphorylation and activation of cytosolic phospholipase A2[22]. Although the exact mechanism remains unclear, there is a suggestion that VEGF may induce melanogenesis by elevating the expression of protease-activated receptor-2 (PAR-2)[23]. Furthermore, endothelin 1, secreted by the endothelial cells of microvasculature, is recognized for its ability to stimulate melanogenesis. It achieves this by activating the microphthalmia-associated transcription factor (MITF) through the activation of endothelin receptor B[24].

Based on accumulated knowledge, it's clear that melasma is not solely an epidermal hyperpigmentary disorder; instead, it is a complex condition with characteristics of photoaging disorders (**Fig. 1**). These factors make it challenging to treat melasma effectively. To address these issues, research efforts have been directed

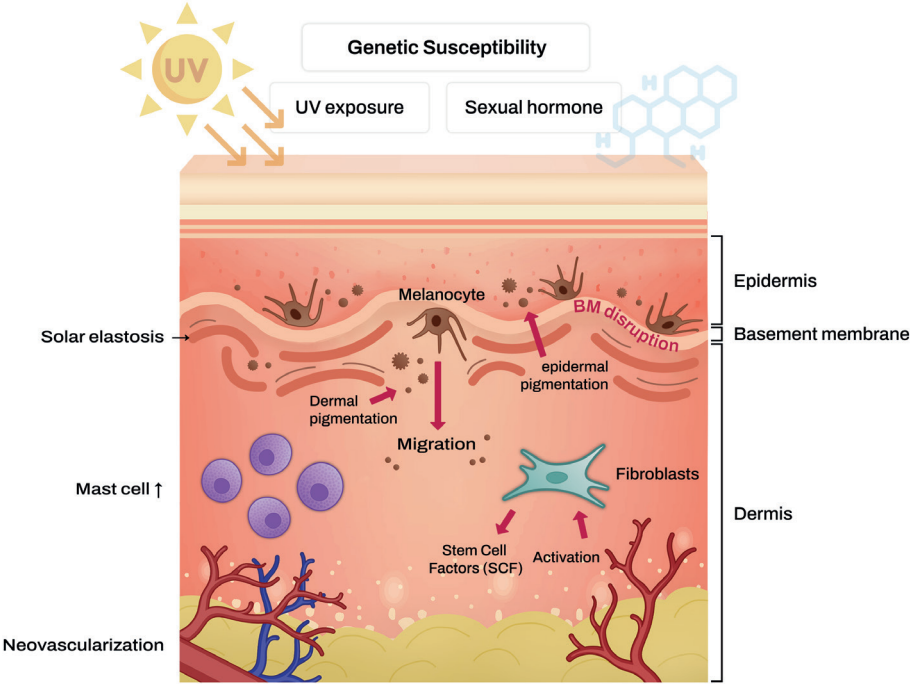

Fig. 1. Schematic representation of melasma pathogenesis.

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toward developing treatments that target the underlying pathophysiology of melasma.

Sunscreen

Wavelength spectrum of solar irradiation is classified as infrared (780–5,000 nm), visible light (VL) (400–780 nm) and UV (290–400 nm) segments[25]. It is well known that both UV and VL exposure cause pigmentary changes, which are explained by physiological mechanism, where generation of reactive oxygen species (ROS) results in release of inflammatory cytokines and matrix-degrading enzymes in the skin. Recent study also revealed that VL induces long-lasting hyperpigmentation via activation of opsin 3-regulated calcium-dependent microphthalmia-associated transcription factor[26]. Together with this finding, photoprotection against VL is important in melasma patients. Indeed, Castanedo-Cazares et al. assigned sixty-eight patients with melasma into two groups to receive either UV-VL sunscreen or UV-only sunscreen randomly[25]. At 8 weeks, the former group showed 15%, 28%, and 4% greater improvements than the latter group in Melasma Area and Severity Index (MASI) scores, colorimetric values, and melanin assessment, respectively. Similarly, Boukari et al.[27] designed another randomized controlled trial comparing two sunscreen groups differed by the presence or absence of iron oxide, an absorbing pigment blocking VL. The authors reported significantly lower MASI score at 6 months in the iron oxide group. Given this converging line of evidence, sunscreen containing either iron oxide or large size (>200 nm) of titanium dioxide and zinc oxide is highly recommended despite undesirable cosmetical issue represented by white turbidity[28].

Topical treatments

1) Skin-lightening agents

Topical skin-lightening agents are mainstream in treating melasma. These compounds target tyrosinase, a rate-limiting enzyme of the melanogenesis pathway[29]. Hydroquinone, one of tyrosinase inhibitors, has solidified for decades as benchmark in the treatment of hyperpigmentation. It is hypothesized that hydroquinone inhibits tyrosinase by binding with the enzyme or interacting with copper molecule at the enzyme's active site. This results in decreased formation of melanosomes, a marked alteration in the internal structure of melanosome, an increased degradation of melanosome, and ultimately, a destruction of the membranous organelles in the melanocytes[30]. Along with this underlying mechanism, indeed, hydroquinone led dose-dependent decrease in pigmentation in the clinical examination, where it was applied topically onto the dorsum of hands with solar lentigines at different concentrations (2%, 3%, and 5%)[31]. Further studies also suggested its skin lightening effect. Ennes et al. compared the proportions showing complete clinical response between melasma patient groups applied with 4% hydroquinone cream and placebo, respectively. The researchers found that there was significant gap between two groups (38% versus 8%)[32]. Despite these accumulated evidences guaranteeing its efficacy, safety issues have been raised continuously, and they often used to make hesitating its use. For instance, concerns regarding the systemic absorption of the drug and drug-induced carcinogenesis have been addressed[33]. Other concerns that several reports of exogenous ochronosis are presumably due to hydroquinone use were also raised[34].

In another perspective, these safety issues have stimulated researchers to excavate novel compounds with a low risk of developing adverse events. 4-n-butylresorcinol, niacinamide, ascorbic acid, resveratrol, azelaic acid and kojic acid were proposed as alternative agents[35].

2) Topical retinoids

Topical retinoids have shown their effectiveness in the treatment of melasma. Retinoids are suspected to stimulate turnover of keratinocytes, inhibit transfer of melanosome, and allow trans-epidermal penetration of other topical therapies[36]. Comparing 0.1% tretinoin cream to vehicle over a 40-week period, Griffiths et al. found that 68% of treatment group showed improvement in colorimetry and histological evaluation versus only 5% of vehicle group. Notably, the effects of this therapy were unclear until 24 weeks and many of treated patients (88%) experienced side effects, including erythema and desquamation[37]. Considering longer treatment required to lead clinical benefit and frequent occurrence of irritation, tretinoin may not be good mono-therapeutic option[38].

Adapalene, a synthetic retinoid, has been applied for melasma patients. Dogra et al.[39] conducted study comparing adapalene 0.1% gel with tretinoin 0.05% cream for Asian Indian melasma patients. The authors reported similar efficacy in both groups, indicated by 37% and 41% reduction of MASI scores in adapalene- and tretinoin-treated groups, respectively with superior tolerability. It was noteworthy that adapalene-treated patients reported quite fewer side effects and its superior tolerability.

3) Combined topical agent

Triple combination cream (TCC), consisted of hydroquinone, retinoid, and topical steroid, is widely used for melasma treatment. Taylor et al.[40] showed its higher efficacy compared with any dual combination of the three active ingredients in a large, multicenter, randomized controlled trial. 77% of TCC-treated participants reached complete or near complete clearing, in contrast only 47% of dual-combination group achieved the very endpoints. Ferreira Cestari et al. also displayed its superiority to 4% hydroquinone in the view of efficacy[41]. Clearance of melasma, meaning lesions nearly equivalent to perilesional skin, was observed in 35% of subjects using TCC versus 5% using HQ alone.

One hypothesis explains the higher efficacy of this product based on the synergistic effects of its ingredients. Specifically, the topical steroid is thought to ameliorate irritation caused by the other two ingredients and inhibit melanin synthesis, while the retinoid is believed to interrupt the oxidation of hydroquinone and facilitate its trans-epidermal penetration[42].

Given that hydroquinone in concentrations above 4% and in treatment courses longer than 3 months may be associated with new onset ochronosis[43], the combination formula limiting the concentration of hydroquinone as 4% thanks to combined effects with other constituents may account for the lower risk of ochronosis[44].

4) Investigational therapeutic approaches

Since academic attempts have unveiled the pathophysiologic mechanisms involved in onset and progression of melasma, various topical agents, targeting each step of cutaneous hyperpigmentation, have been proposed.

Microphthalmia-associated transcription factor-siRNA (MITF-siRNA) cream effectively lightened both brown facial hypermelanosis and normal skin in Asian individuals, by inhibiting the tyrosinase pathway[45].

Topical proton pump inhibitors (PPIs), such as omeprazole, may also inhibit melanogenesis, and present a promising treatment for melasma. Omeprazole topically applied onto the skin of UV-irradiated human subjects elicited significant reduction of pigment levels after 3 weeks compared to untreated controls[46]. It is hypothesized that omeprazole decreases melanogenesis by inhibiting ATP7A and enhancing degradation of tyrosinase. Together with this finding, it is also noteworthy that PPIs may trigger or aggravate vitiligo, supported by the clinical case reports in which patients experienced relapse or development of their vitiligo after the use of oral PPIs[47].

Methimazole is an oral anti-thyroid medication commonly used to treat hyperthyroidism. It is noteworthy that topical application of methimazole causes depigmentation, therefore it can be used for therapeutic purposes in patients with melasma and post-inflammatory hyperpigmentation (PIH). It is believed that methimazole blocks melanin synthesis as a potent peroxidase inhibitor. Kasraee et al.[48] reported moderate to marked improvement of the hyperpigmented lesions with topical methimazole 5% in a 27-year-old male with PIH. Its side effects on thyroid function were neglectable since there were no significant changes in serum thyroid-stimulating hormone, free thyroxine, and free triiodothyronine levels in 20 patients applied by methimazole 5% daily.[49]

Systemic treatments

1) Oral tranexamic acid (TXA)

TXA, originally designed for its hemostatic properties, acts as an antifibrinolytic agent. By interfering with the plasminogen/plasmin system, TXA affects the communication between keratinocytes and melanocytes. Furthermore, TXA hinders the plasmin activity induced by UV light exposure, leading to a reduction in mast cell activity and the inhibition of fibroblast growth factor[50]. This, in turn, results in a decrease in the number of mast cells in the dermis and a reduction in the formation of new blood vessels[13,50]. Moreover, a recent novel study suggested that TXA can activate the autophagy system by increasing the expression of autophagy-related proteins[51]. Earlier research indicates that the autophagy system plays a crucial role in determining skin color by regulating the degradation of melanosomes in keratinocytes, which is enhanced by activators of autophagy[52]. These autophagy-related proteins include Beclin-1, the autophagic modulator WIPI1, and microtubule-associated protein light chain 3 (LC3)[51].

Numerous studies have investigated the appropriate dosage of TXA. Karn et al.[53] reported improved MASI scores in a group that received 500 mg of TXA daily in addition to topical treatments (topical hydroquinone [HQ] with sunscreen) compared to a group receiving topical treatments alone 12 weeks. Eunice et al.[54] demonstrated a 49% reduction in modified Melasma Area Severity Index (mMASI) in a group treated with 500 mg of TXA daily for three months, as opposed to an 18% reduction in a control group applying only sunscreen. Minni et al.[55] showed that in a group receiving 500 mg of TXA daily alongside the application of a triple combination cream, 65.6% of patients experienced a mMASI improvement of 75% or more at 12 weeks, while only 27.1% in the topical treatment-only group achieved this level of improvement. In a study by Lajevardi et al.[56], the combination therapy group, receiving oral TXA at a dosage of 250 mg three times daily in conjunction with 4% HQ, exhibited better outcomes after three months of treatment. The possibility of achieving improved efficacy using higher therapeutic doses has also been explored. In a study by Zhu et al., individuals with melasma were randomly assigned to receive daily doses of TXA at 500 mg, 750 mg, 1,000 mg, or 1,500 mg. There were no significant differences observed in the MASI score or melanin index among the four different dosage groups, although faster results were achieved with higher doses[57]. As the appliance of light- or laser-based therapy on melasma has been increasing recently, several studies about oral TXA use in conjunction with laser therapy have been conducted. The study conducted by Cho et al.[58] reported a more significant reduction in the mMASI score in the group that received a combination therapy of oral TXA at a dose of 500 mg per day along with intense pulsed light (IPL) and low fluence 1,064 nm QS Nd:YAG laser, compared to the group that underwent only IPL and laser treatment. Subsequently, Shin et al.[59] demonstrated that the combined treatment of 750 mg TXA with low fluence QS ND:YAG laser resulted in a higher mean reduction in the mMASI score at eight weeks after treatment compared to treatment with the laser alone.

There are concerns about the thrombogenic risk due to the use of TXA as a hemostatic agent. However, this risk is known to be very low in young adults without underlying medical conditions and who are not taking other medications at the same time[53,56]. However, it is crucial to conduct comprehensive screening for individuals with additional thromboembolic risk factors, including those with cardiovascular disease and current anticoagulant therapy. Such individuals should be contraindicated for systemic TXA therapy.

Despite the relatively good safety profile of oral TXA, there have been attempts to explore different delivery methods. Topical TXA in various formulations, such as gel or solution, has been investigated[60,61]. Moreover, to enhance the efficacy of topical TXA, several strategies have been employed to promote its delivery, including microneedling or CO2 fractional laser techniques[62-64]. Additionally, intradermal microinjection of TXA has also proven to be effective in previous studies[65].

2) Other systemic agents

Others

Polypodium leucotomos (PL) is a tropical fern originating from Central and South Africa[66]. PL is known to have antioxidant effects, anti-inflammatory effects, as well as photoprotective effects by scavenging several ROS and inhibiting the formation of lipid peroxidation[67,68]. Several attempts have been made to utilize oral PLE to treat melasma, but the results have been inconclusive.

Other systemic agents studied for treatment for melasma include Vitamin C, Vitamin E[69,70], Proanthocyanidin-rich extract from grape seeds[71], Korean red ginseng[72], carotenoids[73], or French maritime pine bark extract[74]. Although they have been shown to have beneficial and promising effects on melasma due to their antioxidative effects, the evidence supporting their use is limited, and further research is needed.

Chemical peels

Chemical peels are a well-known treatment option for melasma and are typically considered a secondary approach to managing the condition. Their effectiveness in addressing the epidermal component of melasma is attributed to their ability to induce controlled epidermal separation and subsequent regeneration[75]. Additionally, they may aid in removing stagnant melanin through phagocytosis in the dermal layers[75]. However, it is essential to note that chemical peels carry a substantial risk of causing PIH, particularly in individuals with Fitzpatrick skin types III to VI.

1) Glycolic acid (GA) peels

GA peel is the most commonly used α-hydroxy peel, which has the smallest molecular weight, penetrating the epidermis easily[76]. Several studies have examined the effectiveness of GA peels. However, most of them have not demonstrated any superiority over topical therapy. In a split-face study conducted by Lim and Tham, they compared a combination approach (20%–70% GA peels every three weeks and a topical product containing 10% GA and 2% HQ) to a topical-only treatment. The results showed no significant difference between the two sides[77]. Similarly, in another split-face study conducted by Hurley et al.[78], patients received 20%–30% GA peels every two weeks on one side of their face, along with a twice-daily full-face application of 4% HQ. This study also found no significant difference between the combination therapy and HQ-only treatment.

In contrast, certain studies have demonstrated a promising effect of combining GA peels with topical therapy. Sakar et al.[79] reported a statistically significant improvement in the MASI score 21 weeks after treatment in the group that received 30%–40% GA peels combining TCC compared to the TCC-only group. Similarly, in a study conducted by Dayal et al., the combination of a GA peel with a topical 20% azelaic acid cream showed a statistically significant improvement in the MASI score compared to the topical-only group[80]. However, it is important to note that in the combination group, there were higher side effects such as erythema, a burning sensation, and PIH.

2) Other chemical peels

Various agents, including SA, TCA, and lactic acid, have been explored for chemical peeling in patients with melasma. While the evidence supporting these methods is limited, they could be considered as an option for individuals who have melasma that does not respond well to topical treatments.

Laser and light treatment

Various light devices have been employed in melasma treatment, with IPL demonstrating effectiveness in both standalone and combined therapies, as indicated by several small-scale studies[81-83]. IPL emits a wide spectrum of light (500 to 1,200 nm), making it suitable for various dermatological conditions, including pigmentary disorders. In a study by Choi et al.[82], 30 Asian patients treated with fractionated IPL over 14 weeks exhibited moderate efficacy against melasma. Wang et al.[81] reported IPL's efficacy when combined with TCC and sunscreen, noting the absence of serious side effects. Furthermore, when combined with Q-switched ruby laser (QSRL), MASI scores decreased and were sustained at the 3-month follow-up[83].

Laser therapy, involving various devices like ablative lasers (including CO2 laser and Erbium:YAG [Er:YAG] laser) and nonablative lasers (such as Q-switched Nd:YAG laser [QSNYL], QSRL, and pulsed dye laser [PDL]), has undergone extensive study. However, ablative lasers like CO2 laser and Er:YAG laser are considered prone to postprocedural dyspigmentation[84]. In a study conducted by Hassan et al., melasma patients treated with PDL exhibited

improvements in mMASI scores and a significant reduction in VEGF expression levels[85].

Among the available laser devices, the QSNYL is the preferred choice. In the past, laser treatment for melasma was not recommended due to the risk of hyperpigmentation or hypopigmentation. However, since the introduction of the concept of "laser toning," lasers have been increasingly utilized for melasma treatment. Laser toning involves the repetitively applying a 1064-nm Nd:YAG laser with a large diameter and lower fluence to the melasma-affected areas. This repetitive treatment approach has been popularized for its effectiveness in improving melasma. Furthermore, with the theoretical background of subcellular selective photothermolysis, more physicians have adopted this technique. Kim et al.[86] suggested subcellular selective photothermolysis as the mechanism of "laser toning." They observed dendrite shortening of melanocytes after treatment with 3-dimensional EM. By targeting melanocytes and Stage IV melanosomes, this laser therapy minimizes collateral damage and offers a promising approach to melasma treatment with fewer adverse effects. However, punctate leukoderma has become a concern, and with frequent and repeated treatments, it leads to the destruction of melanocytes[87].

Also, there was a development of a pico-second laser. Feng et al.[88] compared the picosecond and nanosecond Nd:YAG 1064-nm lasers in the treatment of melasma by split-face randomized clinical trial. They concluded that the efficacy is about the same in the treatment of melasma. However, the picosecond laser was less painful during the procedure, with a lower potential risk of exacerbation of melasma.

Moreover, melasma is currently regarded as a photoaging disease[89], and there is a growing trend to combine treatments that target the dermis, given its impact on melasma. In this context, devices utilizing alternative energy sources, such as radiofrequency (RF) devices, exhibit promising results in melasma treatment. In one study, the use of monopolar RF alongside kojic acid demonstrated improved MASI scores. However, the lack of controls limits the interpretation of these results[90]. Microneedle RF, known for minimal epidermal ablation, proves effective in skin rejuvenation and holds potential for treating melasma by enhancing the impaired ECM and promoting melanin elimination[91,92]. Recent research suggests that pulsed-type microneedling RF could be effectively employed for refractory melasma due to its effects, including enhanced permeability for topical treatments and induction of various dermal changes such as alterations in vasculature, melanin washout, and neocollagenesis[93,94].

Clinicians should carefully consider the available evidence and patient-specific factors when selecting the most appropriate treatment modality for melasma, aiming to improve both efficacy and patient satisfaction in addressing this challenging pigmentary disorder. While hydroquinone monotherapy and triple combination cream remain the gold standard for melasma treatment, considering the damaged dermal components of melasma and its challenging characteristics, light-based therapy can be used as an adjunct for treatment. Currently, QSNYL is the first choice in laser treatment, but for recalcitrant melasma patients, light-based therapies targeting the photoaged dermis, such as RF or PDL, should be considered. The treatment modalities affecting dermal components are summarized in **Table 1**.

CONCLUSION

Considering that melasma exhibits characteristics of a photoaging disorder, such as the disruption of the basement membrane, solar elastosis, angiogenesis, and mast cell infiltration in the dermis, it is important that we must take its pathogenesis into account when treating melasma. Various cell types, including melanocytes, keratinocytes, sebocytes, mast cells, and endothelial cells, are involved in melasma. Therefore, when it comes to effectively

Table 1. Treatment modalities affecting dermal components of melasma

Variables	Mechanism	References
Topical		
Hydroquinone	Inhibiting pendulous melanocytes which refer to melanocytes that protrude into the dermal layer and are related to the hyperactivity of melanocytes	95
Retinoid	Decrease in solar elastosis and perivascular inflammation Formation of new dermal collagen	95,96
Azelaic acid	Reversing PUVA-induced senescence of dermal fibroblasts by the activation of PPARγ	35
Oral		
Tranexamic acid	Decrease in the number and activity of mast cells in the dermis Reduction in the formation of new blood vessels	50
Light-based therapy		
Pulsed dye laser	Reduction in VEGF expression levels	85
Microneedle radiofrequency	Enhancing the impaired extracellular matrix	91,92
Microneedle pulsed type radiofrequency	Alterations in vasculature Neocollagenesis	93,94

PUVA: psoralen plus ultraviolet-A radiation, PPARγ: Peroxisome proliferator-activated receptor gamma, VEGF: vascular endothelial growth factor.

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treating melasma, addressing these photoaging-related characteristics should be a priority.

Indeed, a combined treatment approach that includes both epidermal depigmentation and the enhancement of dermal photoaging is expected to be necessary in order to minimize the risk of recurrence in melasma. It is crucial to develop safer and more effective depigmenting agents. Additionally, therapeutic agents or light-based therapies that can restore dermal components, including the disrupted basement membrane or dysregulated dermal components, should be developed.

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The authors have nothing to disclose.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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