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Abstract: Melasma: A Review of Current Treatments

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Melasma is a commonly acquired hyperpigmented skin disorder of uncertain etiology. Several predisposing factors, such as UV radiation, genetic predisposition, dark skin, and female sex hormones, can induce melasma. However, its exact pathogenesis is complex and involves melanocyte function, including interactions between keratinocytes and melanocytes as well as gene regulation abnormalities. Topical therapy remains a mainstay treatment for melasma, and oral medications were helpful in appropriate cases. Procedural approaches, such as laser therapy and chemical peeling, have been proven to be beneficial in most cases. Several recent studies have also suggested new cutting-edge modalities for possible successful treatment, for example, picosecond laser. Besides, this review provides a comprehensive update in the pathogenesis and systematic treatment of melasma (Table 1).

Keywords: Melasma, Pigmentary disorders, Hyperpigmentation, Treatment

บทคัดย่อ

ฝ้าเป็นความผิดปกติของผิวหนังที่เกิดจากการสร้างเม็ดสีเมลานินที่ผิดปกติโดยสาเหตุยังไม่แน่ชัด มีปัจจัยมากมายที่กระตุ้นการเกิดฝ้าเช่น รังสียูวี พันธุกรรม ความเข้มของสีผิว และฮอร์โมนเพศหญิง อย่างไรก็ตามกลไกการเกิดโรคที่แน่นอนมีความซับซ้อนและเกี่ยวข้องกับการทำงานของ melanocytes รวมถึงปฏิสัมพันธ์ระหว่าง keratinocytes และ melanocytes เช่นเดียวกับความผิดปกติของการควบคุมของยีน การรักษาด้วยยาทายังคงเป็นการรักษาหลักสำหรับการรักษาฝ้า ยารับประทานมีประโยชน์ในรายที่เหมาะสม หัตถการบางอย่างเช่น การรักษาด้วยเลเซอร์และการลอกผิวด้วยสารเคมีได้รับการพิสูจน์แล้วว่าเป็นประโยชน์ในผู้ป่วยส่วนใหญ่ โดยบทความวิจัยหลายบทความที่ทำการศึกษาในปัจจุบันยังแนะนำให้ใช้วิธีการที่ทันสมัยที่ใช้ในการรักษาฝ้าได้อย่างมีประสิทธิภาพ เช่น เลเซอร์ picosecond นอกจากนี้ บทความนี้ได้ทบทวนวรรณกรรมที่เกี่ยวข้องกับแนวทางการรักษาฝ้าในปัจจุบันอย่างครอบคลุม พร้อมกับนำเสนอแนวทางการรักษาฝ้าแบบเป็นขั้นตอน

คำสำคัญ: ฝ้า, ความผิดปกติของเม็ดสี, สีผิว, การรักษา

Introduction

Melasma is a chronic acquired hyperpigmented disorder characterized by symmetric poorly defined, brown macules or patches on photo-exposed areas, particularly both cheeks, malar areas, nose, forehead, and upper lip. Although the etiology is unknown, it is triggered by ultraviolet (UV) exposure, the use of oral contraceptives, pregnancy, or stressful events.[1] Notably, melasma is highly prevalent in people with dark skin types, reproductive women, and postmenopausal women. To date, melasma is still a challenging condition to treat and often produces psychological impacts on patients.

Clinical and pathologic features

There are several melasma patterns, among which centrofacial type is the most common. The centrofacial pattern usually presents on the central part of the face, e.g., the forehead, malar areas, nose, cheeks, chin, or upper lip (Figure 1.). For the malar type, the lesions are limit to cheeks, whereas for the mandibular type, the lesions are present on the rami of the mandible. Although unusual, extra-facial melasma can appear in other areas, such as the back, sternum, and forearms. In terms of histologic findings, melasma can present in

three forms, e.g., epidermal melasma, dermal melasma, and mixed type. The pigment in the epidermal form usually deposits on the epidermis and melanocytes are highly dendritic and full of pigment. In contrast, melanin deposits in melanophages in the superficial and middle dermis of the dermal type, while mixed-type melasma can involve both the epidermis and dermis. Also, there is an increase of mast cell and vascularity in the dermis, implying that dermal factors may play essential roles in melasma pathogenesis. Of note, the skin biopsy may reveal significant actinic damages.

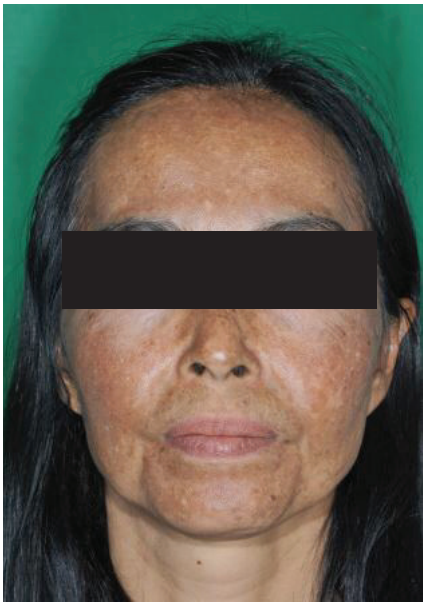

Figure 1. Centrofacial pattern of melasma in a Thai female patient

Etiopathogenesis

The pathogenesis of melasma remains to be elucidated. Melanocytes play a pivotal role in melasma development. Increasing evidence suggests that secreting factors from keratinocytes or fibroblasts nearby contribute to the paracrine effect in melasma development. UV radiation upregulates melanocortin-1 receptors (MC1R) or melanocyte-stimulating hormone (MSH) receptors on melanocytes leading to more melanin production. Keratinocytes also produce proopiomelanocortin (POMC) along with α-MSH and ACTH in response to UV. In terms of hormonal effects, estrogen, and progesterone can induce pigmentation, which is mediated by estrogen receptor-alpha and beta. Presumably, this explains why melasma is more common in post-pubertal women, oral contraceptive users, and during pregnancy. However, the mechanism of female sex hormones involved in pigmentation is not yet clearly understood. In addition, vascular endothelial growth factor (VEGF) can promote human melanocyte survival in cell cultures, suggesting that it is one of the contributing factors of melasma.[2] Although there has been no genome-wide association study to identify associated genes in melasma, genetic factor is considered as a potential risk factor, as some patients' reports on family history.

Current treatments in melasma

Several modalities can treat melasma, for example, topical, systemic, procedural, or combined treatment, all of which involve various aspects including pigmentation, inflammation, vascularity, and photodamage.

Topical Treatment (Table 1)

Sunscreens

UV and visible light account for melanin formation. Sun protection, especially broad-spectrum sunscreen, is a crucial factor in controlling the progression of melasma both in the prevention and enhancing the efficacy of other topical treatments. Evidence suggests that broad-spectrum sunscreen can be applied to prevent the onset of melasma. Furthermore, many patients use camouflage or makeup as additional treatment modalities for their melasma.

Hydroquinone

The most popular treatment for melasma is hydroquinone (HQ). HQ 4% cream can be used as a monotherapy for treating melasma; however, hydroxyquinone combined with tretinoin and topical corticosteroid is more effective. Triple combination therapy (TCT) has a 30% better rate of complete clearing than hydroquinone alone with lower cost in the U.S.[3] Common side effects include irritation and irritant contact dermatitis or dyspigmentation. Caution must be taken as long-term usage can result in exogenous ochronosis.

Corticosteroids

Steroids can inhibit melanogenesis. However, corticosteroids are not recommended as monotherapy due to side effects. Moreover, current studies show that corticosteroids alone have no long-term benefits in melasma treatment.

Tretinoin

Retinoids are mostly used to promote the absorption of HQ. Tretinoin modulates keratinocyte pigments, interferes with the transportation of melanin pigment, stimulates keratinocyte turnover, inhibits tyrosinase, and interrupts the synthesis of melanin. Tretinoin is effective but often irritates. Another synthetic retinoid with less irritation, adapalene, can be used as an alternative retinoid in melasma patients. Topical retinoids and adapalene should be avoided during pregnancy.

Topical combination therapy

Although HQ is an effective monotherapy, the greater outcome is evident when HQ is combined with retinoid and corticosteroid. Kligman''s formula is a popular combination for treatment. The original formula contains 0.1% tretinoin, 0.1% dexamethasone, and 5% hydroquinone. Additionally, tretinoins have an antioxidative effect of preventing the oxidation of HQ. Dexamethasone was used to relieve irritation induced by HQ or tretinoin. Improvement is evident within three weeks after the twice-a-day application. Also, modified Kligman's HQ formula was created for appropriate skin types to reduce tretinoin-induced irritation and decrease steroid side effects.

Other topical whitening agents

Azelaic acid

Azelaic acid is a reversible competitive tyrosinase inhibitor.[4] It possesses anti-inflammatory, anti-keratinization, anti-bacterial, and anti-pigmentation properties. Moreover, it is shown to suppressPUVA-induced cell aging in human fibroblasts.[5] Azelaic acid has been approved for melasma, postinflammatory hyperpigmentation, as well as acne treatment.[4]

Kojic acid

Kojic acid acts by chelating copper at the active site of tyrosinase enzymes. However, Kojic acid is less effective as a monotherapy.[5] In a split-face study, glycolic acid with kojic acid preparation shows no significant superiority but more irritation compared to glycolic acid with hydroquinone preparation.

Ascorbic acid

Ascorbic acid or vitamin C interacts with copper at the active site of tyrosinase, similar to kojic acid (Table 1). Topical ascorbic acid is unstable and is usually combined with licorice extracts and soy to increase its efficacy. It is less effective as a topical monotherapy. A study shows that ascorbic acid monotherapy is less effective than that of HQ in improving MASI scores.

Arbutin

Arbutin is a natural compound derived from bearberry, cranberry, and blueberry.[6] It is another tyrosinase inhibitor and inhibits melanosome maturation.[5] Deoxyarbutin, however, is a more potent tyrosinase inhibitor, and it is shown to be more effective.

Licorice extract

Its active ingredients are liquiritin and isoliquiritin. Licorice extract possesses an anti-inflammatory and antioxidant effect. Likewise, this naturally occurring compound has been shown in some studies to decrease pigmentation by inhibiting the tyrosinase enzyme.[7]

Systemic treatments (Table 1)

Tranexamic acid (TA)

The tranexamic acid used in melasma is off label. TA is a plasmin inhibitor, available in oral, topical, and injectable forms. Oral TA is pregnancy category B and is used in pregnant women with bleeding disorders. TA blocks plasmin production, thus, it decreases arachidonic acid and prostaglandin levels, thus it prevents the activation of melanocytes. Recent studies show that TA also decreases VEGF and ET-1; both may contribute to vascularity in melasma.[8] However, there is no consensus on the optimal dose for treating melasma. Practically, the dosage usually ranges from 500-750 mg

daily.[8] A systematic review and meta-analysis shows an improvement in the MASI score after treatment with TA. Side effects, including hypo-menorrhea, mild abdominal discomfort, and transient skin irritation, are minor. Severe side effects, such as deep vein thrombosis, are possible but rare. The topical formulation of TA has been reported as effective as HQ.

Glutathione

Glutathione is a tripeptide and also a potent antioxidant.[9] Glutathione also employs other mechanisms to decrease melanogenesis, including chelating copper ions to inactivate tyrosinase and shifting the production of eumelanin to pheomelanin.[9] A randomized controlled study of 60 healthy Thai medical students who received 500 mg glutathione in 2 divided doses for four weeks show a significant decrease in melanin indices, determined by Mexameter®.[10]

Polypodium leucotomos (PL)

This tropical fern native to Central and South America has antioxidative and immunomodulatory effects.[11] Recent studies show that PL can interfere with melanogenesis by reducing UV-induced photodamage and ROS inhibition.[12] PL has been used as adjunctive therapy in melasma with favorable results.[11]

Procedural treatment

Chemical Peeling

Superficial peelings such as glycolic acid (GA) are typically chosen as adjunctive therapy due to the benefits of epidermal turnover and lower complication risk. In a recent review, chemical peels show good results in melasma patients. GA 70% peel compared to tretinoin 1% peel at a 2-week interval for four sessions shows a remarkable reduction in MASI score in a study for both groups, notwithstanding lacking statistically significant difference.[13] However, chemical peels usually cause PIH due to irritation or inflammation. Trichloroacetic acid (TCA) peels 10–20% shows similar efficacy to GA; however, TCA produces slightly more adverse effects, including irritation.

Laser and light treatment

Laser therapy becomes an alternative treatment for melasma in recent years. Many studies investigated laser treatments with variable outcomes. However, this therapeutic modality is challenging and causes frequent complications such as PIH, particularly in darker skin types. Thus, non-ablative lasers are preferable in terms of less inflammation and subsequent PIH.

Intense pulsed light (IPL)

IPL can treat many pigmentary disorders with its long wavelength between 515 nm and 1,200 nm. A randomized controlled study of 17 patients treated with IPL for four sessions shows a better reduction in MASI than that of the hydroquinone-only group.[14] Fractional IPL offers an alternative treatment for conventional IPL with favorable outcomes.

Q-switched lasers

Q-switched lasers target the melanin in the epidermis and dermis selectively. Q-switched lasers have been recently investigated in various studies with variable successes. However, many studies show that when the laser is used as monotherapy, a high recurrence rate and poor long-term outcome were common.[15-16] Some studies have demonstrated better pigmentation improvement, and less PIH with low fluence Q switched neodymium: yttrium-aluminum-garnet (Nd: YAG).

Fractionated resurfacing lasers

Fractional resurfacing, either an ablative fractional laser or a non-ablative fractional laser, can be used to treat melasma. Non-ablative fractional laser is preferable as the scarring and dyspigmentation are lesser and can be used for the treatment of dermal melanocytic lesions, dermal melasma, and nevus of Ota.[14] Many recent studies show the efficacies of 1,550 nm NAFL in melasma treatment.[14] Despite higher PIH, ablative fractional resurfacing lasers, including CO2 lasers and erbium: YAG lasers, have been reported to be a favorable melasma treatment. A study using low-fluent CO2 laser compared with Q-switched Nd: YAG shows superior results with fractionated CO2 laser arm without significant differences in adverse reactions, partly reflecting the beneficial dermal remodeling effect of CO2 laser.[17]

Pulse dyed laser

Given that angiogenesis and vascularity may contribute to the development of melasma, PDL is a potential therapeutic option. In a split-face randomized prospective study, 18 Caucasian women using a 4-month combination of triple therapy with PDL therapy shows an outstanding decrease in the MASI score.[17] However, a randomized clinical trial with Copper Bromide laser versus triple combination topical therapy showed no statistically significant result in their efficacy.[18] Overall,

vascular targeting with laser therapy seems to show beneficial outcomes in some melasma patients, but its significant benefits remain questionable.

Picosecond lasers (PL)

Picosecond lasers (PL) are a recent ground-breaking laser innovation, which is available in 532 nm, 755 nm, and 1,064 nm laser output. PLs generate picosecond pulses, resulting in much shorter pulse durations, thereby causing pigment fragmentation by photoacoustic rather than photothermal effects. PLs also generate effective removal of pigments without thermal damage to the neighboring tissue.[19] Initially, PLs have been used for tattoo removal with encouraging results and low adverse reactions.[19] Recently, various studies have demonstrated that PLs are an effective and safe treatment for melasma.[20-22] However, more robust clinical studies are required to assess the role of PLs in melasma.

Summary

The etiopathogenesis of melasma is not yet fully understood. The mainstay treatment in melasma is a topical treatment in which combination therapies provide greater efficacy than monotherapy. Sun protection remains the most important prevention for melasma. Among many whitening agents, hydroquinone is still a gold standard treatment and effective in melasma. For recalcitrant cases, topical therapy together with systemic agents and laser and light therapy might provide a better outcome (Figure 2.). Laser treatments seem to be alternative options with promising results. Therefore, A good understanding of the etiology and pathogenesis of melasma enables us to develop more effective therapies in the future.

Table 1 Melasma treatments, mechanism of action and adverse effects

Modality	Source	Active compounds	Mechanism of actions	Adverse effects
Sunscreen protection	Synthetic	Zinc Oxide, TiTanium Dioxide, Oxybenzone, Octocrylene, Octinoxate, Octisalate	Inhibit UVA, UVB, visible light	None
Hydroquinone	Synthetic	1,4-dihydroxybenzene	Tyrosinase inhibitor	Irritation, dryness, erythema, rebound effect exogenous ochronosis
Corticosteroids	Synthetic	Corticosteroids	Inhibit endothelin-1(ET-1), inhibit granulocyte-macrophage colony-stimulating factor (GM-CSF)	epidermal atrophy, telangiectasia, irritation, steroid acne, perioral dermatitis
Tretinoin	Synthetic	Retinoic acid	Tyrosinase inhibitor, disperse keratinocyte pigment granules, melanosome transfer inhibition, accelerate epidermal turnover	Irritation, scaling, erythema
Azelaic acid (AA)	*Pityrosporum ovale*	9-carbon dicarboxylic acid	Reversible competitive tyrosinase inhibitor, Inhibition of ROS, inhibition of mitochondrial activity in hyperactive and abnormal melanocytes	Pruritis, mild erythema and scaling, burning sensation (mild and transient)

Table 1 Melasma treatments, mechanism of action and adverse effects (continue)

Modality	Source	Active compounds	Mechanism of actions	Adverse effects
Ascorbic acid	Fruits, vegetables	L-ascorbic acid (LAA)	Tyrosinase inhibitor, Antioxidant	Irritation, erythema, dryness (rare)
Kojic acid	Fungi (*Aspergillus oryzae, Penicillium spp*)	5-hydroxy-2-hydroxymethyl-4-pyrone	Tyrosinase inhibitor (copper chelation)	Irritation
Arbutin/ deoxyarbutin	Bearberry plant (*Arctostaphylos spp, Bergenia crassifolia)*	Beta-D-glucopyranoside	Tyrosinase inhibitor, melanosome maturation inhibition	None
Licorice extract	Legume root (*Glycyrrhiza glabra*)	Glabridin, Liquiritin, Isoliquiritin	Tyrosinase inhibitor, antioxidant	None
Niacinamide	Amide form of vitamin B3	Active amide of Niacin (Vitamin B3)	Reduces transfer of melanosomes from melanocytes to keratinocytes	Irritation
Soy	Soybean	Soy trypsin inhibitor (STI), Bowman-Birk inhibitor (BBI)	reversible inhibit protease-activated receptor-2 (PAR-2) pathway	None
Tranexamic acid (TA)	Synthetic derivative of amino acid lysine	Trans-4-Aminomethylch clohexane-carboxylic acid	Block plasmin production, reduce alpha-melanocyte stimulating hormone (α-MSH) decrease vascular endothelial growth factor (V-EGF), endothelin-1(ET-1)	Abdominal bloating/pain, Nausea/vomiting headache, hypomenorrhea/ oligomenorrhea
Glutathione (GSH)	Synthetic	γ-glutamyl-cysteinylglycine	Tyrosinase inhibitor (copper chelation), antioxidant, shifting the production of eumelanin to pheomelanin	(No long-term GSH use)
Polydium Leucotomos (PL)	Tropical fern native to Central and South America	Cinannamic acid (phenolic acid)***	Antioxidation, immunomodulatory effect, reduce UV-induced photodamage	None
Glycolic acid	Synthetic/Natural	α-hydroxy acid	Epidermal remodeling, activate desquamation	Irritation, post-inflammatory hyperpigmentation (PIH)
Micro-needling therapy	n/a	n/a	Remain unclear (facilitate the transport of therapeutic drugs)	Erythema, infection, PIH
Laser treatment	n/a	n/a	Photoacoustic effect, Photothermal effect	PIH

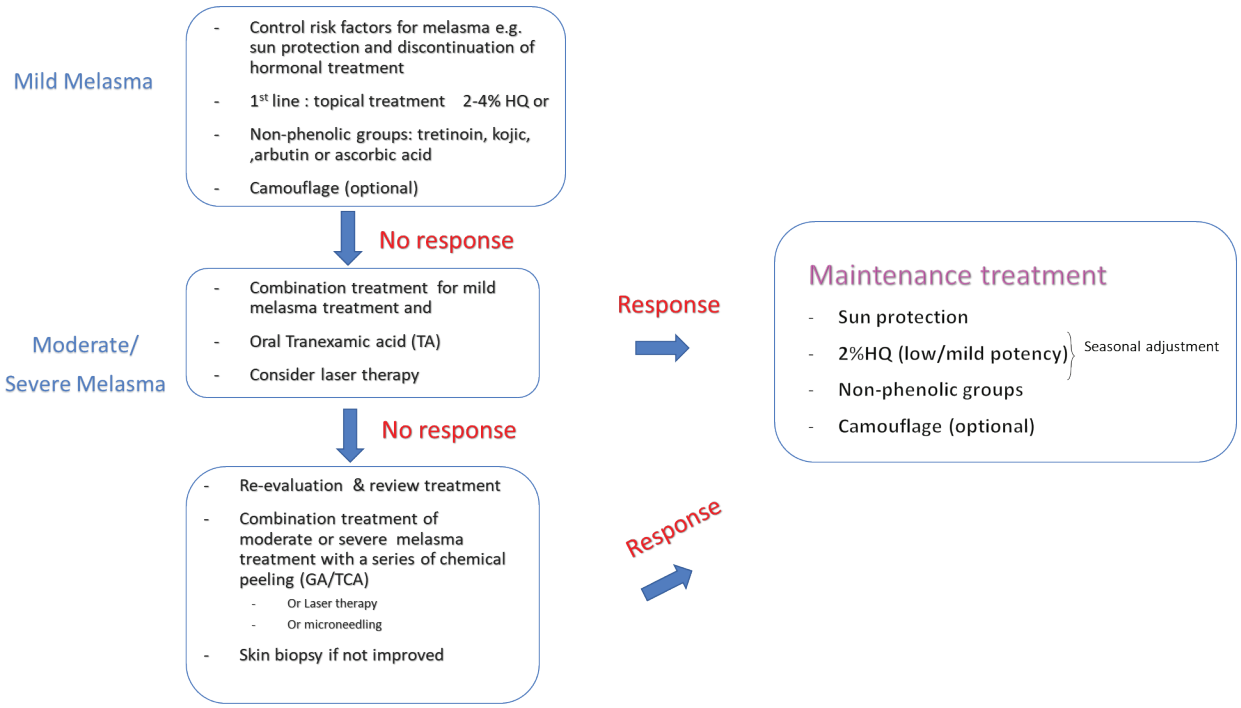

Figure 2. Therapeutic Ladder in melasma

A proposed therapeutic algorithm for melasma treatment based on literature review and expert opinion.[23-25]

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