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An Overview on Melasma

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Abstract

Melasma is a common pigmentary skin disorder, characterized by symmetrically-distributed hyperpigmented patches with serrated, irregular and geographic borders. It usually affects the chronically photo-exposed cutaneous areas, especially the face and neck. Its exact worldwide prevalence is unknown. The disease most commonly occurs in women of reproductive ages.

The etio-pathogenesis of melasma is not completely understood. This disorder seems to be an interplay of various internal and environmental factors. Among these factors, genetic predisposition, sunexposure and hormonal factors are the most important ones.

In this article, in addition to the introduction of melasma, we have tried to review the most effective medications and modalities for the treatment of this common, refractory, pigmentary disorder.

Keywords: Melasma; Pigmentation; Pathogenesis; Treatment

Introduction

Melasma is an acquired,chronic,recurrent hyperpigmentary disorder. The word "melasma" is derived from the Greek "melas", which means black color. The condition is also known as "chloasma", another Greek term which means green in color, or mask of pregnancy, referring to the high prevalence of the disease in pregnant women. Melasma is clinically characterized by symmetric light-brown to bluish-gray macules and patches, with irregular,sharp borders. The pigmentation may be guttate, linear or confluent [1,2].

Melasma usually affects the chronically photo-exposed cutaneous areas, especially the face and neck. On the face, the forehead, cheeks, temples, upper lip, chin or nose are commonly involved. More rarely, lesions may afflict extensor arms and sternal region. Although this disorder has been considered a benign condition, which usually has only aesthetic implication, it may affect self- image and self-esteem, with a negative impact on patient's quality of life [1,2].

Epidemiology

Melasma is a common pigmentary disorder, affecting about 5-6 million individuals in the United States. However, its exact worldwide prevalence is unknown. It can affect patients of both sexes and of all races and ages. The disease is most commonly described in women of reproductive ages. In men, melasma is rare and represents less than 10% of all cases [3].

Melasma is more common in darker-skinned patients with Fitzpatrick skin types IV to VI, who live in world areas of high-intensity ultraviolet radiation (UVR). It is more prevalent in Hispanic, Asian and Afro-descendant. The age of onset is usually between 30-55 years; rarely the disease has been described during puberty or in post-menopausal period [4,5].

Etiology and Pathogenesis

The etio-pathogenesis of melasma is complex and not completely understood. It appears that this disorder is an interplay of various internal and environmental factors, which may be responsible in triggering, maintaining or relapsing lesions. Among these factors, genetic predisposition, sun-exposure and hormonal factors are the most important ones, all of which significantly increase the tyrosinase activity [6].

Genetic predisposition has been suggested by the evidence of a familial history and the association with particular races [7]. Studies have shown that the genes related to lipid metabolism such as PPARα, ALOX15B, DGAT2L3 and PPARGC1A are less expressed in melasma [8].

The role of the UVR has been well established in the development of melasma. This role is supported by the following points:

Localization of the lesions on the sun-exposed areas

The higher prevalence of melasma in the world areas of intense UVR

Accentuation of the lesions in the summers and their attenuation in the winters [7,8]

Effectiveness of the broad-spectrum sunscreens in preventing and treating melasma,

The immunoistochemical features of cutaneous sun damage (e.g. solar elastosis) [7]

Studies have shown that whole sun-light spectrum including UVA (320-400 nm), UVB (290-320 nm) and visible light are important in the pathogenesis of melasma [9]. They act through the following mechanisms:

Increasing the melanocyte proliferation and activity

Promoting transfer of the melanin pigments to the keratinocytes [10]

Promoting inflammatory mediators [10,11]: The UVR causes peroxidation of lipids in the cellular membranes, leading to generation of free radicals, which promotes the melanocytes to produce excess melanin [9-11].

Up-regulating expression of the melanogenic mediators from the keratinocytes and dermal stem cells [11,12]: The UVR induces production of alpha-melanocyte stimulating hormone [α-MSH],which lead to an increased melanocytosis and melanogenesis [10- 12].

Up-regulating protease-activated-receptors [11]

Inducing angiogenesis [12]

The female sex hormonal activity has an important role in the pathogenesis of melasma, especially in women. The association of this disorder with pregnancy,oral contraceptive pills and hormone replacement therapies in post-menopausal, is well-known [13]. Studies have shown that melanogenesis is stimulated by the luteinizing hormone (LH), follicle-stimulating hormone (FSH) [13] and placental sphingolipids [14].

Histopathology

Generally, the histopathological features of melasma per se are subtle, so that control skin biopsies are necessary for comparison and subsequent diagnosis [15].

In this disorder, rete ridge flattening and epidermal thinning have been observed [16]. Studies have shown that the epidermal melanocytes in the lesional skin are more active than that in the normal skin [9,17-26]; hence, the increased epidermal melanin is its pathological hallmark [18,22,23], seen significantly in the basal and suprabasal cells as pigmentary caps [9,15] (Figure 1). In some studies, this finding has been observed in all layers of the epidermis [15]. Moreover, the stratum corneum is thinned [16] and in some cases, degraded molecules of the melanin have been observed in this layer [27] using Masson Fontana for staining the melanin pigments [15,22]. For showing increased melanocytic activity, the Mel-5 immuno-staining is administered [15]. More precise assessment shows enlarged, intensely stained melanocytes with prominent dendrites [15,17,20-23,28].

Assessment of the basement membrane shows that it is disrupted in melasma and in comparison with the normal perilesional skin, expresses significantly less of the type IV collagen and markedly more of the MMP2 protein and mRNA [18,20]. Moreover, the staining is negative for MMP9 [20]. These findings show that the chronic UVR can be responsible for the loosening of basement membrane in melasma via up-regulating the MMP2 expression [18]. These features are more evident at the margin of some melanocytes, leading to a feature of protruding into the dermis,termed pendulous melanocytes [18,20]. These findings are also seen in other epidermal hypermelanoses related to hyperactivity of the melanocytes such as cafe´-au-lait spots, senile lentigo and intense UVA-irradiated skin and even normal black skin [20]. These pendulous cells can easily drop into dermis [11].

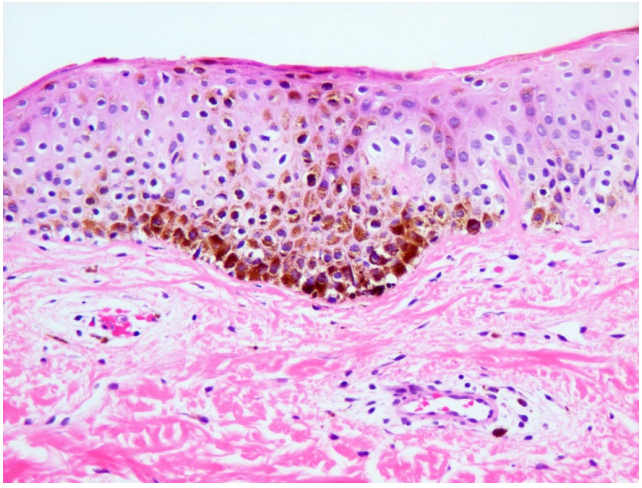

Figure 1: Pathology of melasma.

In the dermis, melanin pigments are seen in two forms:

Mainly in macrophages (melanophages) and

As free melanin deposits around the superficial and deep dermal vascular plexuses [15]. However, it appears that the significance of dermal melanin in melasma is controversial, because some studies have shown that the amount of dermal melanin, in comparison with the perilesional normal skin is not significant. Moreover, while dermal melanin is less detectable in Caucasian melisma and frequently found in melasma patients with Fitzpatrick skin types III to V, it is detectable as the normal findings in the normal facial skin of some races such as Korean and Japanese. On the other hand, it has been suggested that alterations in dermal structures has a role in the melasma development, so that a network of cellular interactions between the fibroblasts, vasculatures and melanocytes during the chronic sun exposure can lead to stimulating the melanocytes [18].

In melasma, some non-specific changes can be observed such as solar elastosis [15,16,18-23], increased vasculature and telangiectasia [15,16,18,20-22,29]. Solar elastosis, a predominant findings in the melasma lesions [18], is seen as clumps of thick and fragmented elastic fibers in the papillary dermis,stained with Verhoeff-van Gieson [15]. In this pigmentary disorder, there is a mild perivascular lymphohistiocytic infiltrate [28]. In contrast to post inflammatory hyperpigmentation [PIH], there is no apparent inflammatory phase in all stages of its development [30].

Immunohistochemistry studies have shown that the number of epidermal melanocytes can be both increased and normal in the lesional skin [23,28]. These studies have also shown that the protein expression levels of some genes including tyrosinase, TYRP1, TYRP2 and MITF are increased in the melasma lesions [18,22]. Additionally,the melanocytes are intensely NKI beteb [20,22] and α-MSH- immunostained [23]. In the dermis,immunohistochemistry study for the vascular markers shows increased numbers of the vessels in the upper parts. It appears that there is a positive relationship

between the number of vessels and epidermal pigmentation in melasma [18].

Electron microscopy studies have revealed that the melanocytes are filled with more melanosomes, mitochondria, Golgi apparatus, rough endoplasmic reticulum and ribosomes, reflecting the increased melanocyte activity [17]. Studies have shown that the lesional skin of melasma has different biophysical characteristics, including skin barrier function [16].

Clinical Manifestations and Classification

Melasma affects exclusively the sun-exposed areas. It commonly occurs in the face and occasionally the neck and forearm [24,28]. During and after periods of the sun exposure, its clinical manifestation is more apparent [28].

The melasma patches have serrated, irregular and geographic borders [28] distributed in a symmetrical manner [24,25]. According to clinical manifestations, three patterns of melasma have been recognized:

Centrofacial [6,9,28,31-33]

This pattern is the most common type of clinical manifestation of melsma, involves the forehead, cheeks, upper lip, nose and chin [6,28]. This pattern is seen in about 65% of the cases [19,34].

Malar [6,9,28,31-33]

This pattern affects the cheeks and nose [6,28],and is seen in about 20% of the melasma cases [19,34].

Mandibular [6,9,28,31-33]

The ramus of the mandible is the site of involvement in this pattern [6,28]. It has been reported in about 15% of patients [19].

Extra facial [19]

It commonly involves the extensor surface of arms and forearms, neckline, upper third of the dorsal area of the trunk and sides of the neck [19,34]. It is prevalent in some populations with special characteristics in relation to its probable etiopathogenic factors [35].

Regarding the pathological view three types of melasma have been introduced:

Epidermal

Dermal

Mixed [31,36]

Under the Wood light examination,four types of melasma have been identified (Figure 2):

Epidermal [6,15,28,32,37]

This type is the most common pattern of melasma [15,28]. In this type, the melanin is increased in the whole epidermal layers,and a few scattered melanophages can be seen in the papillary dermis; hence, under the Wood light examination,pigmentation is intensified [28]. The epidermal type is seen in about 70% of the patients [19].

Dermal [6,28,32,37]

The most of the melanophages can be observed in the dermis; hence, the pigmentation is not enhanced under the Wood light examination [6,28]. This type has been reported in 10 to 15% of the cases [19].

Mixed [28,32,37]

In this type, there are both of increased melanin in the epidermis and increased melanophages in the dermis; hence, under the Wood light examination, in some parts,there is enhancement of pigmentation while in another parts, there is no change [6,28].

Indeterminate [6,9,28,32,37]

This type is seen in the individuals with the skin type VI, because the Wood light has no benefit in examining these patients [6,9,28].

Studies have shown that the correlation between the clinicopathological manifestations of melasma and the findings acquired by the Wood lamp examination is controversial [15,19,22],because the Wood lamp underestimates the dermal melanin deposition [28].

Diagnosis and Differential Diagnosis

The diagnosis of melasma is often based on the clinical features, but this method is not satisfactory, because there are many pigmentary disorders that clinically mimic melasma. These different skin hyperpigmentations and melasma mimickers have varying etiologies; therefore, to select an effective therapeutic regimen, diagnosis of melasma should be accurate. For the accurate diagnosis, histopathological examinations and subsequent clinical correlation are invariably required [15].

The following is the list of some of the most important skin dyspigmentations that should be considered in the differential diagnosis of melasma.

Lichen planus pigmentosus [15]

It is a variant of lichen planus, characterized by bilaterally symmetrical gray blue patches or plaques affecting the sun-exposed areas, especially the neck and adjacent torso. This pigmentary disorder is prevalent on the Indian subcontinent and the Middle-East. Photosensitivity is observed in some patients. Under the Wood light examination, its lesions are not enhanced, because hyperpigmentation is mainly dermal [15].

Discoid lupus erythematosus [DLE] [9,15]

It is characterized by hyperpigmented plaques on the sun-exposed areas. Melanotic LE is a rare variant of DLE, characterized by hyperpigmentations that arise de novo without preceding inflammatory manifestations, clinically indistinguishable from melasma and lichen planus pigmentosus. Bilateral asymmetry and follicular plugs are clues in the clinical diagnosis of DLE. Under the Wood light examination, DLE lesions are accentuated [15].

Phototoxic dermatitis [19,28]

It is resulted from photochemical reactions between the UVR and phototoxic agents administered topically or orally. Topical psoralens

and several drugs are in the list of these phototoxic substances [28]. Berloque dermatitis or au-de-cologne dermatitis is a kind of phototoxic dermatitis, resulting from topical application of the phototoxic oil of bergamot and related substances found in perfumes and other cosmetics [19,28]. The lesions start as erythema and blisters after sun exposure, developing into post-inflammatory hyperpigmentation. In mild cases, hyperpigmentation in a streaked pattern is seen with little or no erythema phase [28].

Phytophotodermatosis [19]

This dermatosis is secondary to contact with plants containing furocoumarins or psoralens, which involves the sun-exposed areas. Regarding the amount of contacting substance, its lesions can be asymptomatic or have itching and burning. In this disorder, unlike allergic photodermatitis, pruritus is not a common symptom [19].

Erythema dyschromicum perstans (Ashy dermatosis,gray dermatosis or dermatosis cinecienta) [19,28]

It is an idiopathic chronic skin disorders, characterized by oval and round blue-gray patches affecting the trunk, proximal extremities and rarely the face and neck [28]. It is most frequently seen in women and children on their first decade of life [19].

Early lesions of ashy dermatosis may have a raised, erythematous border that soon disappears. Pruritus has been reported in skin lesions [28]. The exact cause of ashy dermatosis is unknown, but some factors such as ingestion of ammonium nitrate, orally administered X-ray contrast media, exposure to chlorothalonil, exposure to environmental contaminants [19,28], chronic hepatitis C infection, HIV and vitiligo have been reported as its etiology. It appears that an immunologic mechanism is involved in pathogenesis of ashy dermatosis [19,28].

Flagellate dermatosis [19]

It is characterized by pruriginous, urticarial erythematous linear streaks evolved to characteristic hyperpigmentation, most commonly involving the trunk. Although it is a specific reaction to bleomycin, some similar cases have been seen after ingestion of shiitake mushroom (Lentinus edodes) [19].

Pigmented contact dermatitis (Riehl melanosis) [15,18,28]

It is characterized by patches of diffuse gray-brown pigmentation on the temples, forehead [15,18,28],scalp and neck [15,18]. Erythema, scaling or pruritus have occasionally been reported in this disorder [15]. Allergens in cosmetics, fragrances, kumkum [15,28], henna [15] and coal tar dyes, particularly brilliant lake red R and other 1-phenylazo-2-naphtholderivatives are the common causes for Riehl melanosis. It appears that the UVR through the induction of photocontact dermatitis plays an important role in pathogenesis of this disease [28].

Acquired bilateral melanosis of the neck in peri-menopausal women [18]

It is a dermal melanocytotic or melanotic hyperpigmentation, characterized by bilateral, symmetrical brown to gray patchy or mottled pigmentation, exclusively involving the neck. It is particularly common in Asians women in peri-menopausal period. It appears that this disorder represent a continuum of Riehl's melanosis [18].

Erythromelanosis follicularis faciei [28]

It is a rare skin disorder, characterized by irregular red-brown telangiectatic pigmented patches affecting the preauricular regions, cheeks and less commonly the neck. Within the patches, there are pale follicular papules with loss of vellus hairs. Keratosispilaris of the upper extremities and trunk is often accompanied erythromelanosis follicularis faciei. No photosensitivity has been reported [28].

Poikiloderma of Civatte or cervical idiopathic poikiloderma [9,15,19,28]

It is a common cutaneous pigmentary disorder, characterized by combination of telangiectasia, dyspigmentation and superficial atrophy in a reticular pattern [15,19,28]. It affect symmetrically the sun-exposed parts of face, neck and V of the chest [15]. Characteristically, it doesn't affect the area shaded by the chin [19,28]. Poikiloderma is most frequently seen in postmenopausal Caucasian women [15]. The chronic sun exposure, genetic predisposition, hormonal factors in combination with the normal aging process, photosensitizing chemicals in perfumes or cosmetics have been implicated in the pathogenesis of Poikiloderma [19,28]. Its lesions are usually asymptomatic; rosacea like symptoms [28], discreet burning and pruritus [19] have been reported by small percentage of patients. This disorder, has a chronic, benign, but irreversible course [19,28].

Drug-induced hyperpigmentation [6,8,9,11,15,28]

It is characterized by brownish colorations, often with a blue-gray hue mainly effecting the sun-exposed areas and mucous membranes (particularly the mouth, conjunctivae) [28]. Drugs can cause skin hyperpigmentation through the following mechanisms:

Stimulating epidermal melanocytes, either directly or indirectly [6,11,28].

Stimulating nonspecific cutaneous inflammation, which is worsened by the sun exposure [6].

Impairing the melanin clearance from the skin via binding to the melanin molecules and creating a stable complex [11,28].

Accumulation of the triggering medication itself in the skin [11].

Stimulating synthesis or deposition of some special pigments under the influence of the drug [28] such as deposition of lipofuscin- ceroid [11,15] and redox dye secondary to clofazimine administration [15].

By deposing iron secondary to the drug-induced damage to the dermal vessels [9,11,28].

Sometimes, more than one mechanism is implicated in inducing skin hyperpigmentation [28]. The tetracyclines (particularly minocycline) [6,8,15,28], tricyclic antidepressants (particularly imipramine and desipramine) [28], antimalarials [6,8,15,28],cytotoxic drugs [6,15], phenothiazines (mainly chlorpromazine), anticonvulsants, amiodarone [6,8,28], clofazimine [15] and sulfonylureas [8] are included in the list of drugs inducing hyperpigmentation [28]. Clofazimine induced pigmentation is brown-colored, accentuated in the sun-exposed areas, sometimes indistinguishable from melasma. Typically, these lesions are generalized along with the nail involvement [15].

Fixed drug eruption is a clinically distinctive type of drug-induced hyperpigmentation, characterized by recurrent plaque[s] at fixed locations. It most frequently involves the lips, genitalia and acral areas.

Many drugs can cause this disorder, but the most important are barbiturates, ibuprofen and sulfonamides [15].

PIH [6,18,19,30,34]

This dyspigmentation, characterized by increased pigmentation secondary to a cutaneous inflammatory process [6,19,34], is more commonly seen in the races with darker skins [18,19,30]. Its most common causes include acne [6,19,30], atopic dermatitis, allergic or irritant contact dermatitis, trauma, psoriasis, lichen planus [6,19,34], discoid lupus erythematosus, morphea, pityriasis rosea, polymorphous light eruption, erythema dyschromicum perstans [34], vesiculobullous diseases such as bullous pemphigoid and herpes zoster [6,34], drug eruptions, cosmetic procedures [19], ingrown hairs, scratches, insect bites, sun burning and surfactant damage [30,34]. Its pathogenesis is still not completely known, but it appears that it is more related to the nature of the triggering inflammation [19]. It is probably caused by increased melanogenesis or abnormal distribution of the melanin, secondary to the action of cytokines, inflammatory mediators and oxygen reactive species [19,30,34].

Ephelides (Freckles) [15]

They are manifested as irregular, discrete, small pigmented macules, affecting the sun-exposed areas, specially the nose and malar areas. Their pigmentation varies based on seasons and level of sun exposure [15].

Solar (actinic) lentigos (lentigines, age spots or liver spots) [30]

These lesions, characterized by dark spots, involve sun-exposed areas, particularly the hands, arms and face. Chronic exposure of skin to UV and the resultant chronic inflammation are the most probable cause of this pigmentary disorder [30].

Acanthosis nigricans [15,19]

This disorder is characterized by symmetrically hyperpigmented, velvety thickening of the skin, mainly affecting nape of the neck and flexural areas of the body and less commonly the face, back of hands, fingers, palms, tongue and lips [15]. Recently, 8 subtypes of this disorder have been identified including benign, obesity-related, syndromic, malignant, acral, unilateral, secondary to medication and multifactorial [19].

Macular amyloidosis [15,19]

This dermatosis is a variant of the cutaneous amyloidosis [15,19], most commonly affects women in the Middle-East and India. It is characterized by symmetrical pruritic dark-browns rippled or reticulated pigmentations occurring on the central, upper back, chest, extremities and face. Its lesions are not photosensitive and under the Wood light examination, there is no accentuation [15].

Nevus of Ota [18]

It is a well-known dermal melanocytoses, characterized by blue-grey pigmentation and occurs almost exclusively in the Asians [18].

Hori's Nevus (Acquired bilateral nevus of Ota like macules) [15,18]

It is an acquired condition, characterized by blue-brown or slate gray macules or patches, bilaterally affecting the malar, cheeks, forehead, temples and eyelids. The ocular and mucosal membranes are not involved in this disease [15]. Hori's nevus that occurs almost exclusively in the Asian population [18], frequently affects elderly women. These lesions are not photosensitive and under Wood light examination, there is no enhancement [15].

Becker's Nevus [15]

It is an acquired melanosis, characterized by hyperpigmented patches and plaques with variable degree of hypertrichosis, presented in the vicinity of the large joints especially the shoulders, elbows and hips. Its onset is in late childhood or early adolescence [15].

Argyria [15]

The characteristic manifestation of this disease is a gray-blue discoloration, effecting the sun-exposed areas, ear cartilage, nails, mucous membranes and sclera. It results from prolonged ingestion of silver such as silver-coated sweets, silver-coated cardamom, beetle nut and fennel seeds (as mouth freshners). In localized form, argyria is caused from prolonged contact with silver. Under the Wood light examination, these lesions are not enhanced [15].

Ochronosis [15,38]:

Exogenous ochronosis is characterized by asymptomatic hyperpigmentation, erythema, papules and nodules on the sun-exposed areas of body, caused by prolonged use of topical bleaching creams containing hydroquinone [38]. This disorder predominantly involves the bony prominences, lower jaws, forehead, temples, nose, sides of neck [15], upper chest and upper back. It appears that oxidation and polymerization of by-products from hydroquinone result in ochronosis [38].

Endogenous type of ochronosis (alkaptonuria), characterized by deposition of polymerized homogentisic acid in the connective tissues of skin and internal organs, is an autosomal recessive disorder caused by inherited deficiency of homogentisic acid oxidase [15].

Confluent Reticulate Papillomatosis of Gougerot-Carteaud [15,19,39,40]

It is an uncommon skin pigmentation, manifested by bilaterally symmetrical coalescing brown papules and plaques in a reticulate pattern [15]. This disorder involves the upper chest, upper back, shoulders and neck [39]. Its etiology is unknown. It more frequently involves women, aged 10 to 35 years [19]. Its diagnostic criteria include in:

macules and brownish desquamative spots, with reticulated and papillomatous aspect,

involvement of the upper chest and neck,

negative testing for fungal infections,

no response to antifungal drugs and

significant response to minocycline [19,40].

Facial hypermelanosis secondary to systemic disorders:

Addison disease [9,28]

This disease, caused by primary adrenocortical insufficiency, is characterized by weakness, nausea, vomiting, diarrhea and hypermelanosis. In Addison disease, hypermelanosis occurred in two forms:

Changes in intensity of the normal skin pigmentation

Development of new areas of pigmentation in the gingival or buccal mucous membranes

Melanogenic action of the increased blood levels of certain pituitary peptides is implicated in the pathogenesis of hypermelanosis in Addison disease [28].

Hemochromatosis [28]

In this common genetic disorder, iron is deposited in different organs, resulting in a whole spectrum of systemic manifestations. Cutaneous pigmentation in this disease is characterized by a slate gray or gray-brown discoloration involving most frequently the sun exposed areas, such as the face and back of the hands. Spotty intraoral pigmentation, ichthyosis like changes, alopecia and koilonychia are other skin manifestations observed in this disease [28].

Porphyria cutanea tarda [28]

This disease is characterized by skin changes including hyperpigmentation, bullae, atrophic scars, milia and hirsutism. In this disease, facial hyperpigmentation is in differential diagnosis of melasma [28].

Associated and aggravating factors

Studies have shown that the melanocytes are not the only cells involved in melasma. These studies have revealed that other factors probably have a key role in the development and the relapses of melasma. Identifying these associated factors is important for obtaining a more efficient treatment and better prevention of the relapses [41]. Some of the most important of these factors have been stated in the Table 1.

Although the familial predisposition and genetic component is the most important risk factor for the development of melasma, no Mendelian pattern of segregation has yet been identified. It appears that the genetic factors may be related to the stimulation of melanogenesis [8].

The UVR is an important predisposing factor in the melasma development [19,26]. The pigmentation of this disorder usually improves in the winters and worsens in the summers [7,8,42]. It appears that the action mechanism of this radiation is through inducing melanocortin within melanocytes and keratinocytes [19]. Sunscreens that only block the UVB are unsatisfactory because the longer wavelengths (the UVA and visible radiation) also induce melanogenesis [9].

Melasma is more common in the individuals with darker complexions [9,37] and prevalent in the Hispanic, Asian and African-American women. A global study by Ortonne et al. showed that lighter-skinned patients in comparison with darker-skinned patients were less likely to have any relatives with melasma. They also confirmed that the patients with the family history of melasma had darker skin. Furthermore, they showed that the individual with the positive family history less likely had the onset of melasma triggered by the use of hormonal contraception [43].

Factors	References
Genetic factors	[3,8,19,22,23,32-34,37,41,43,44,45]
Family history	[4,8,19,22,23,43]
Gender	[19,33,46]
Age	[19,22,23,33]
Skin type	[4,19,30,33,37,44,47]
Ethnic group	[8,9,43,44]
Sunlight exposure	[3,8,9,19,21-23,26,32,34,37,41,43-45,47,48]
Menstruation	[43]
Pregnancy	[3,8,19,21-24,30,33,34,37,43,44-47]
Lactation	[49]
Age at first pregnancy	[43]
Age at puberty	[43]
Administration of hormonal contraceptions	[3,8,19,21-23,30,32-34,37,41,43,44,46]
Hormone therapy	[3,9,33,34,37,41,43,45-47]
Corticosteroid therapy	[8]
Hormonal factors	[3,9,22,48]
Ovarian dysfunction and tumors	[9,36]
Testicular dysfunction	[3]
Thyroid dysfunction	[3,8,9,24,46,33,47]
Liver disease	[3,8,36]
Administration of phototoxic and anti-seizure drugs	[3,8,19,24,32,33,37,44,45,47]
Cosmetics administration	[3,8,9,19,32,33,36,45]
Chronic long standing illnesses	[3]
Nutritional disorder	[3]
Consumption of certain food items	[8]
Parasitic infestation	[3,8]
Occupation	3
Living in areas of intense UV radiation	[3,19,37]
Stress	[8,32,37]

Table 1: The most important associated and aggravating factors of melasma

Later, Hexsel et al. in an epidemiological studies on Brazilian patients showed that the age of melasma onset was related to the skin phototypes and family history, so that the skin types II and III and the

family history of melasma was associated with early onset of the disorder when compared with the skin types IV, V and VI [4].

Melasma afflicts 10-15% of pregnant women [23]. Ortonne et al. have shown that melasma appearing for the first time during a pregnancy increases with multiple pregnancies [43]. It has been shown that an increase in placenta, ovarian and pituitary hormones such as α-MSH, oestrogen and progesterone are the causes of pregnancy-associated melasma [8,9,23,43].

In women, later puberty increases the risk of pre-menopausal onset of melasma. It has been reported that in a small group of patients, melasma worsens during menstruation [43].

In a study by Sarkar et al., it was revealed that melasma in men in comparison with that in women, is more frequently associated with the genetic factors and sunlight [3]. Studies have shown that men with melasma have significantly increased circulating LH and markedly decreased testosterone in comparison with men without melasma; hence it has been suggested that there is a subtle testicular resistance in men with melasma [3,8]. In women, differences in the levels of 17-β-estradiol at the beginning of the menstrual cycle have been reported in the melasma cases and it appears that this circulating estrogen may constitute a risk factor and 'maintainer' of the disorder. The association of melasma with the thyroid disorders is controversial [8].

Some patients report the onset of melasma after stressful episodes and affective disorders. Stress is effective in the melasma induction through influencing on the release of propiomelanocortins such as ACTH [8] and MSH [8,37].

The extra-facial melasma is related to the menopause [4,35], family history and personal history of facial melasma. It appears that this type of melasma is not associated with the use of the medications or hormone therapies [35].

Specific Investigation

When approaching a patient with melasma, a detailed history should be obtained. It is important to assess any family history, personal history of melasma and if the patient had been experiencing any therapy for melasma in the past, the administered therapeutic regimen and its efficacy [50].

At the next step, regarding this history, laboratory tests such as the complete haemogram, stool examination, sex hormones, liver function tests [3], thyroid function tests, adrenocorticotropic hormone, cortisol, serum vitamins and serum iron [44] are requested. In countries with high prevalence of the thyroid diseases, these disease should be ruled out because it can interfere with the melasma treatment outcomes [37].

Prevention

Patients should be advised to avoid the sun-exposure, particularly at the peak radiation times [37,47]. When sun-exposure is unavoidable, they should use broad-spectrum sunscreen, cover up and wear a wide-brimmed hat [37]. In these cases, sunscreens with a sun protection factor [SPF] greater than 30 and with physical photoprotective agents in their formulation are recommended [19]. Patients should be encouraged to avoid scented cosmetic products for facial cleansing or makeup [6]. In cases that the hormonal contraceptives or hormone replacement therapy is responsible for melasma, alternative therapies should be considered [6, 37].

Treatment

To achieve the most effective and suitable treatment and/or procedure for the patients with melasma, determination of the severity of melasma is important [37]. Additionally, studies suggest that the melanin pigments and blood vessels should be targeted for obtaining the effective treatment of melasma [18,51,52]. Different therapeutic modalities inhibit the melanin production or dispersion at variable stages through a variety of mechanisms [11,53].

Some of the most important mechanisms of medications and modalities in treating melasma including:

Inhibiting the tyrosinase [11,29,54]:

The tyrosinase is a glycoprotein within the membrane of melanosomes that catalyzes several oxidative reactions required for the melanin synthesis from tyrosine [11,55]. Most of the whitening agents have a tyrosinase-inhibiting effect resulting in the reduced total melanin production, such as kojic acid, arbutin and different kinds of vegetal or herb extracts [55]. These agents are classified as competitive, uncompetitive, mixed type and non-competitive inhibitors. Most of these agents show reversible inhibition of the enzyme [54].

Preventing the maturation or intracellular trafficking of tyrosinase [54]

Some whitening agents act through influencing the tyrosinase mRNA at the transcription levels [54].

Inhibiting the tyrosine hydroxylase and DOPA-oxidase activities [29,55]

Some whitening agents like arbutin and deoxyarbutin are effective in treating melasma through inhibiting the tyrosine hydroxylase and DOPA oxidase activities [55].

Inhibiting the peroxidase [50]

This enzyme is important in the final steps of melanogenesis. Some medications such as topical methimazole is a potent peroxidase inhibitor and can be used in treating melasma [50].

Inhibiting the pigments [54]

Some whitening agents can prevent the induction of pigment [54].

Acting as melanin degrading enzymes [54]

The melanin pigments are degraded enzymatically in the keratinocytes. Some whitening agents are effective in treating melasma through degrading the pigments [54].

Inhibiting the melanosome transfer [11,29,55]

Once the melanosomes are formed in the epidermal melanocytes, they are transferred to the neighboring keratinocytes [11]. Some whitening agents such as nicotinamide, soybean and soymilk extracts prevent the melanosome transfer [55] through inhibiting the keratinocyte protease-activated-receptors 2 [11,55].

Anti-inflammatory activities [11,29,54]

The melanogenesis is enhanced by the inflammatory mediators. These mediators perform via variable mechanisms including:

Stimulating the melanocyte cell growth and dendrite proliferation, such as the leukotrienes C4 and D4 and prostaglandin E2.

Promoting the melanin production, such as the interleukin-1, interleukin-6 and reactive oxygen species.

Damaging the melanocyte cells, resulting in aberrant transfer of the melanosomes into the dermis [11].

SMA-432 is a prostaglandin E2 inhibitor, which has been used in treating melasma successfully [50].

Antioxidant activity [11,29,54]

The reactive oxygen species can induce the melanogenesis in the skin by activating the tyrosinase as the enzyme prefers superoxide anion radical [O_2^-] over O_2 and direct photo-oxidation of pre-existing melanin [55]. Antioxidants such as vitamins E, C and B are effective as whitening agents through reversing this process [54,55].

Melanocytotoxic activity [29]

Some of agents act through melanocytotoxic activity in treating melasma lesions [29].

Targeting vascularization [22,52]

Some therapeutic modalities such as the pulsed dye laser [PDL] are effective in the treatment of melasma through this way [22,52]. Additionally, by targeting the vascularization and at least some part of elastosis in the lesions, the stimulation of melanocytes and subsequent relapses are decreased [22].

Accelerating the epidermal turnover and desquamation [55]

Some of whitening agents such as tretinoins and peeling agents act via increasing the desquamation leading to the removal of excessive melanin content within the skin. Additionally, these agents accelerate the epidermal turnover [55].

Decreasing the expression of MIFT gene [55]

The MIFT, the main factor of regulatory network of transcription factors and signaling pathways, plays an important role in controlling the survival, proliferation and differentiation of melanoblasts and melanocytes. Some of depigmenting agents such as some flavonoids like resveratrol are effective in treating melasma via suppressing the expression of this gene [55].

Blocking glutaminergic receptors [55]:

These receptors have been shown to specifically affect the MITF expression and lead to melanocyte hyperproliferation; hence, they can be an appropriate targets for skin-lightening ingredients [55].

Targeting Toll-like receptor 7 (TLR7) [56]

Studies have shown that the normal human melanocytes express this receptor. Imiquimod is effective in the treatment of melasma by inhibiting the melanogenesis and cell growth through the TLR7-mediated mechanisms [56].

Regulating β2-adrenoreceptors and catecholamines [55]

The epidermal melanocytes express the β2-adrenergic receptors that its activation increases the melanin synthesis. It has been shown that blockage of these receptors can reduce the risk of UV-induced melanogenesis [55].

Inducing the 6(R)-L-erythro-5, 6, 7, 8-tetrahydrobiopterin (6BH4) [55]:

This molecule plays an important role in the melanogenesis through acting as rate-limiting cofactor for phenylalanine hydroxylase and tyrosinase hydroxylase and allosteric inhibitor for tyrosinase [55].

Regulating the sex hormones [55]

Although studies have shown that the epidermal melanocytes are oestrogen responsive, the effect of oestrogen on pigmentation is controversial [55].

Inhibiting adrenocorticotropic hormone and α-MSH [54]

These hormones stimulate the pigment production; hence, via their inhibition, we can treat hyperpigmentation disorders [54]. Undecylenoyl phenylalanine is a novel skin-lightening agent, acting as α-MSH and beta-adrenergic receptor (β-ADR) antagonist. In a study, Katoulis et al. administered this compound successfully in the treatment of melasma in females [57].

Suppressing growth of melanocytes [54]

The Wnt/β-catenin pathway plays an important role in the developmental process of melanocytes [54]. Studies have shown that the lesional skin of melasma expressed high levels of the Wnt inhibitory factor-1 [WIF-1] compared with the perilesional normal skin [21,58]. By suppressing this pathway, the melanocytes growth and melanin production can be inhibited [21,54,57].

The sun protection is a mainstay in the treatment of melasma, because without strict sun protection, all treatments for this pigmentary disorder fail [9,11,25,28,37,59]. Sunscreens containing physical blockers like zinc oxide and titanium dioxide are more effective than chemical blockers because they have broad-spectrum protection [9].

In comparison with the dermal and mixed-type melasma, the epidermal type responds better to topical therapies because many topical therapies are not able to target the dermal melanophages [11,60]. It has been shown that conventional hydroquinone therapy or triple combination therapy still remains the most efficacious and cost effective treatment for melasma, particularly in the patients with darker skin [28,61,62]. In severe, refractory cases, a combination of topical agents with or without in-office procedures, with different mechanisms of actions are required [33,53,63].

Some of the medications and therapeutic modalities administered for the treatment of melasma include in:

Hydroquinone

Hydroquinone is a phenolic compound with two important derivatives including monobenzyl and monomethyl ether of hydroquinone 38]. It is found in tea, wheat, berries, beer and coffee [55].

Hydroquinone is the gold standard for the treatment of melasma [32,37,44-46,50,59,60,64,65], commonly used at concentrations of 2-4% [9,38]. It is effective in treating melasma through the following mechanisms

Inhibiting the tyrosinase [6,9,11,32,34,37,44,64]

Hydroquinone competitively suppresses the melanin synthesis through inhibiting the sulfhydryl groups and acting as a substrate for the tyrosinase [38]. Additionally, this agent through the generation of reactive oxygen species and quinones can result in the oxidative damage of tyrosinase [55].

Inhibiting the melanocyte DNA and RNA synthesis [6,11,34,37,38,55,64]

Because of this action mechanism of hydroquinone, its carcinogenic effect should be considered [38].

Damaging the melanosomes and melanocytes [6,34,37,38,55,64]

Semiquinone free radicals released during the hydroquinone action can damage the melanosomes and melanocytes [38].

To treat melasma, most frequently hydroquinone is used in combination with retinoids and corticosteroids in the Kligman's formulation (5% hydroquinone, 0.1% tretinoin, 0.1% dexamethasone) and the modified Kligman's formulation (4% hydroquinone, 0.05% tretinoin, 1% hydrocortisone acetate) [38,66].

The first triple formulation which received the Food and Drug Administration approval for the treatment of melasma consists of hydroquinone 4%, tretinoin 0.05% and the low-potency class VI corticosteroid fluocinolone acetonide 0.01% (Tri-Luma® cream) [37,64,66]. In addition to optimizing the melasma therapeutic outcomes [67], this formulation has successfully been used for preventing the melasma recurrence [67-69]. In long-term therapy, it is more appropriate to consider adding antioxidants instead of corticosteroids to the combination of hydroquinone and retinoids [70].

Hydroquinone is transported rapidly from the epidermis into the vascular system, detoxified within the liver [55]. The most important side effects of hydoquinone include in skin irritation, allergic contact dermatitis [11,32,37] and in the chronic uses, exogenous ochronosis [6,9,11,32,34,37,38,45,50,64], pigmented colloid milia [32,38], sclera and nail pigmentation, pseudo yellow nail syndrome, cataract, loss of elasticity of the skin, impaired wound healing, exuding an offensive fish odor [38] and transient or permanent depigmentation [55,64]. In studies on animals, its carcinogenicity has been observed, but clinical studies has not proven this side effect in humans [11,64].

Arbutin

Arbutin is the b-D-glucopyranoside derivative of hydroquinone [38,64] and derived from the dried leaves of a number of different plant species including, bearberry (Arctostaphylos uva-ursi), blueberry, cranberry and pear trees [38,55]. Its mechanisms of action in treating melasma include in:

Inhibiting the tyrosinase activity, competitively [38,54,55].

Inhibiting the tyrosine hydroxylase and DOPAoxidase activities [55].

Inhibiting the melanosome maturation [38].

Arbutin at high concentration causes paradoxical hyperpigmentation [38]. In comparison with hydroquinone, arbutin is less cytotoxic to melanocytes [38,55,64] and in comparison with kojic acid, it is less effective in treating hyperpigmentations [71].

Deoxyarbutin is a synthesized topical derivative of arbutin [38,64,71]. In the treatment of melasma, it causes an enhanced sustained improvement, general skin lightening and a safety profile comparable to hydroquinone [71]. While the protein expression of tyrosinase is not affected by arbutin and hydroquinone, an effect on this protein level is seen with deoxyarbutin [55]. However, deoxyarbutin has less melanocyte cytotoxicity in comparison with arbutin and hydroquinone [54,55].

Mequinol

Mequinol is a derivative of hydroquinone, used in the treatment of melasma [38,64]. Its mechanism of action is through inhibiting the tyrosinase and subsequently suppressing the formation of melanin precursors [38].

In comparison with hydroquinone, mequinol is more effective with lesser side effects [29, 7]. It has been marketed in the USA at a concentration of 2% in combination with 0.01% tretinoin for the treatment of melasma. Side effects of this combined formulation include erythema, desquamation, skin irritation, pruritus and halo hypopigmentation [38]. In a clinical trial, Keeling et al. administered this combination successfully in treating melasma in men [72].

Rucinol

Rucinol [4-n butyl resorcinol] is a phenolic derivative, effective in treating melasma through inhibitingthe tyrosinase and tyrosinase-related protein (TRP-1) [29, 37]. It is the first substance shown to inhibit these two molecules simultaneously, leading to significant reduction of pigmentation scores [37].

N-acetyl-4-S-cysteaminylphenol

N-acetyl-4-S-cysteaminylphenol is a phenolic compound, effective in the treatment of melasma [38]. In comparison with hydroquinone, it is more stable and causes less irritation [38, 64]. Its mechanisms of action include:

Inhibiting the tyrosinase activity [38].

Decreasing the intracellular glutathione by interfering with the thiol system, favoring the pathway of pheomelanin at the expense of eumelanin formation [64].

Retinoids

Retinoids are derivatives of vitamin A, used in the treatment of melasma as monotherapy or in combination forms [33,38,59,63]. Retinoids as monotherapy are so very slow in response [9,11]. In

combination with hydroquinone and corticosteroids, retionoids reduce the rate of corticosteroid-induced atrophy and facilitate the epidermal penetration and delivery of hydroquinone [37,38]. They have the following mechanisms in treating melasma:

Inhibiting the tyrosinase [11,32,34, 37,38,44,64].

Inhibiting the tyrosinase transcription [55].

Inhibiting the epidermal melanin dispersion [11,37,38,64].

Increasing the keratinocyte turnover, thereby accelerating the pigment loss by shedding the epidermis [6,9,11,32,37,38,44].

Reducing the amount of time cells to acquire the pigment [6,37].

Interfering with the pigment transfer to the keratinocytes .

Increased the stratum corneum compaction along with decreasing the melanin content [38].

Irritation, erythema, desquamation [11,32,38] and paradoxical hyperpigmentation [9,32] are the most common side effects of retinoids. In comparison with tretinoin, adapalene has less adverse effects in the treatment of melasma [32].

Azelaic Acid

Azelaic acid, a saturated dicarboxylic acid, is found naturally in wheat, rye and barley and produced by pityrosporum ovale, a yeast strain [55]. Azaleic acid is effective in the treatment of melasma through the following mechanisms:

Inhibiting the tyrosinase [6,11,32,37,64]: This compound can acts as competitive inhibitor of the tyrosinase [55].

Inhibiting the melanocyte proliferation [6,11,34,37]: Azelaic acid has anti-proliferative and cytotoxic effect on the abnormal melanocyte [6,55] through inhibiting the thioredoxin reductase [55].

Suppressing the reactive oxygen species [11,32]

Anti-inflammatory and anti-keratinizing activity [37]

Interfering with the DNA synthesis and mitochondrial oxidoreductase [6,64]

Azelaic acid targets only the hyperactive melanocytes; hence, it does not lighten skin with the normally functioning melanocytes [9,32]. It has been shown that 20% azelaic acid is significantly more effective than 2% hydroquinone at lightening melasma [63,73].

Irritation, erythema, pruritus [6,11,32,34,37] and scaling [32,34] are the most important side effects of this agent. In rare cases, acneiform eruptions, telangiectasia, asthma, vitiligo and hypertrichosis have been reported with this agent [37].

Kojic Acid

Kojic acid [5-hydroxy-2 hydroxymethyl-4-pyrone] is a hydrophilic fungal product derived from certain species of Acetobacter, Aspergillus and Penicillium [38,55,64]. It is administered in the treatment of melasma at concentrations of 1% to 4% [38]. Its mechanisms of action include:

Inhibiting the production of free tyrosinase [38].

Inhibiting the tyrosinase [6,11,32,34,37,38,55,64].

Suppressing the tautomerization from dopachrome to DHICA [64].

Scavenging reactive oxygen species [11]: Kojic acid is a potent antioxidant [6,38].

Sensitization and irritation are side effects of this agent [6,37,64].

Antioxidants

A variety of antioxidants have been introduced for treating melsma [29,33,39,74]. These antioxidants have been prescribed as monotherapy or in combination forms in treating this refractory skin disorder [29,33,39].

I- Ascorbic acid or vitamin C is a well-known antioxidant which is used as a lightening agent in oral and topical forms [6,29]. Because of the unstable nature of this agent, its topical forms are prepared in esterified forms, of which the most popular is magnesium-ascorbyl-phosphate [6,38] followed by ascorbyl-6-palmitate [38]. It is formulated with chemical penetration enhancer for treating melasma [29]. Its mechanisms of action in the treatment of melasma include:

Interacting with the copper ions at the tyrosinase active site.

Inhibiting the melanogenesis via acting as reducing agent in various oxidative steps of the melanin formation [38].

Alpha tocopherol or vitamin E is the major lipophilic antioxidant in humans, that can be effective in the treatment of melasma through the following mechanisms:

Photo-protective activity.

Interfering with the lipid peroxidation of melanocyte membranes.

Increasing the intracellular glutathione content.

Inhibiting the tyrosinase [38].

Inhibiting the tyrosinase hydroxylase activity [6].

In a study, Hayakawa et al. revealed that the topical vitamin E in combination with topical vitamin C can be more effective than topical vitamin E alone in treating melasma [75]. Allergic and irritant reactions are the only side effects reported rarely in administration of topical forms of this vitamin [38].

Zinc, as an anti-oxidant and anti-inflammatory agent and with its peeling and exfoliating properties reduces melanin production. The zinc in oral and topical formulations is effective in the treatment of melasma [29]. In an open clinical study, Sharquie et al. showed the efficacy of zinc sulfate cream on improving melasma [76].

Niacinamide

Niacinamide or vitamin B3 is the physiologically active amide of niacin, found in yeast and root vegetables [55,64], required for the cellular metabolism. The efficacy of this substance in treating melasma is though the following mechanisms:

Inhibiting the melanogenesis via interfering with the interaction between keratinocytes and melanocytes [38].

Modulating the protease-activated receptor [PAR-2], subsequently interfering with the transfer of melanosomes from melanocytes to surrounding keratinocytes [38,54,55].

Administration of niacinamide concurrent with sunscreens can be effective in inhibiting the hyperpigmentation and increasing lightness of the basal skin color [77].

Corticosteroids

Corticosteroids are used in the triple-agent creams for treating melasma [37,51,64]. Their mechanism of action in the treatment of melasma is not completely known [32,37,64]. Some mechanisms are including:

Directly affecting the melanin synthesis [32,37].

Altering the melanocyte function without killing them [37] which explains their short-lived effects.

Inhibiting the prostaglandin or cytokine production by epidermal cells [32].

The most important dermatological side-effects of corticosteroids include atrophic changes, perioral dermatitis, rosacea, acneiform eruptions and telangiectasia [32,37,64]. On the other hand, it appears that these agents can exacerbate melasma through inducing telangiectasia which is a component of melasma [51].

Tranexamic acid

Tranexamic acid [Trans-4-Aminomethylcyclohexanecarboxylic acid] is a synthetic derivative of lysine, administered to prevent the abnormal fibrinolysis leading to reduced blood loss. As a plasmin inhibitor, it reversibly blocks the lysine binding sites on the plasminogen molecules, thus inhibits the plasminogen activator from converting plasminogen to plasmin. Studies have shown that the plasminogen also exists in human epidermal basal cells, induced by the UVR leading to the melanogenesis [17]. Tranexamic acid has the antiplasmin activity and subsequently inhibits the melanin synthesis via decreasing the α-MSH [29]. It appears that the oral contraceptive pills and pregnancy activate the process of melanogenesis through increasing the serum plasminogen activator [17].

Studies have shown that tranexamic acid, in oral, topical and injectable forms, decreases the melasma severity [17,28,33]. For the first time, Maeda et al. colleague in 1998 reported that this substance has a dose-dependent preventive effect on pigmentations in the sun-exposed areas, not in the unexposed areas [78]. Its mechanisms of action include:

Inhibiting the UV- induced plasmin activity in the keratinocyte through preventing the binding of the plasminogen to the keratinocyte, leading to decreased the production of prostaglandins and subsequently reduced melanogenesis in the melanocytes [17].

Suppressing the keratinocyte- activate-melanocyte pathway [17]: To be explained, the plasmin can induce the single chain urokinase PA secretion from the keratinocytes; this later protein can induce the tyrosinase activity, increased cell perimeter area, increased dendrites and keratinocyte growth, differentiation and migration. Additionally, the growth of keratinocytes surrounding the melanocytes has an important role in the melanin synthesis. Tranexamic acid can be effective in the treatment of melasma with blocking these pathways [17].

Decreasing the tyrosinase activity [17].

Decreasing the tyrosinase-related protein TRP1/2 [17].

Reversing the melasma-related dermal changes such as vessel number [18].

This substance has no effect on the number of melanocytes and length of their dendrites. Generally, studies have shown that tranexamic acid is the only modality actually preventing the melanocytes' activation by the sunlight, hormonal influence and injured keratinocyte via inhibiting the PA activation system. Additionally, this substance not only reduces the formation of melasma, but also reduces the likelihood of recurrence after other therapeutic agents [17].

Mild irritation and potential risk of intravenous infection and cardiac overload are the only side effects reported in treatment with this substance in the forms of topical formulation and intravenous injection, respectively. Nausea, diarrhea, orthostatic reactions, anaphylactic shock, skin reaction, acute renal corticalnecrosis and disturbances in color vision are the reported side effects with oral forms. Notably, no effect on coagulation parameters has been reported with tranexamic acid therapy. This substance has no mutagenic and harmful fetal effects [17]. Because tranexamic acid is stable agent against warmth, oxidation and UV irradiation, it can be used an ideal option for composition in skin lightening creams [29].

Antisense Oligonucleotides

Antisense oligonucleotides are effective in the treatment of melasma through modulating the synthesis of key enzymes of melanogenesis, including the tyrosinase, TRP1 and TRP2 by interacting with targeted mRNA at translational level. Additionally, it has been demonstrated that these agents acts via decreasing the enzyme activity of DOPA oxidase [29].

Botanical Products

Today, topical agents containing biologically active ingredients are appropriate alternatives to standard depigmenting products, because they are safe, often inexpensive and available over the counter [11,29]. Although irritation with them is less than that seen in the conventional therapies, allergic and phototoxic reactions are more seen with this agents [11].

The botanical agents, in the forms of plant extracts, herbal preparations and isolated plant-derived compounds, can be used orally or topically in treating or preventing melasma. The botanical therapies are consistently effective in treating the epidermal melasma, but their efficacy is variable in the treatment of dermal types. They are significantly beneficial in the individuals with risk factors for this disorder such as the chronic sun exposure or a family history of dyspigmentation [11].

Flavonoids are benzopyrene derivatives [29], found in most of botanical extracts [11]. These substances are classified into flavones, flavanols, isoflavones, flavanones and anthocyanidins [29]. Although the flavonoids suppress the melanogenesis through acting as a substrate competitor for the tyrosinases, antiradical activity and subsequent inhibiting reactive oxygen species formation [29,55], in vitro studies have shown some flavonoids such as citrus naringenin can increase the melanogenesis in melanoma cells [11,55]. It appears that not only the depigmenting factors of flavonoids are relatively free from side effects, but also they have anti-inflammatory, anti-irritant, anti-allergic [29,64], anti-oxidant, anti-viral and anti-carcinogenic properties [38,55] .

Licorice [11], orchid [11,29,38,79] and marine algae [38,80], coffeeberry [38,81], mulberry extracts [38] are effective in the treatment of epidermal melasma.

Licorice extract, derived from the root of Glycyrrhia Glabra Linnera, improves hyperpigmentation by dispersing the melanin, inhibition of the melanin biosynthesis and decreasing the free radical production [38]. Additionally, this agent has anti-inflammatory properties by inhibiting the superoxide anion and cyclooxygenase activity [82].

Soy can reduce the epidermal pigment [11,74]. Genistein and diadzein which are primary metabolites of soy have the active ingredients, so-called soy trypsin inhibitor and Bowman Birk inhibitor, are effective as whitening agents through inhibiting melanosome transfer to the keratinocytes and antioxidant activity [29]. Soy affects the cytoskeletal and cell surface organization, leading to reduction of keratinocyte phagocytosis [55]. Furthermore, it contains active ingredients like isoflavones and vitamin E, which are effective in treating melasma [38].

Studies have shown that epigallocatechin gallate is the most potent phenolic agent found in green tea [29,38]. It has been demonstrated that this agent modulates melanin production in dose-dependent manner [29]. In addition, this has anti-inflammatory, anti-oxidant and anti-carcinogenic effects [38].

Proanthocyanidin is a powerful antioxidant, extracted from grape seed [38]. Studies have shown the efficacy of oral proanthocyanidin in treating melasma [83,84].

Aleosin is another botanical agent, derived from aloe vera, which is effective in the treatment of melasma [29,38,85]. It acts through competitively inhibiting the hydroxylation of tyrosinase to the DOPA and the oxidation of DOPA to the dopachrome [29,55,64]. Aleosin which is a C glycosylated chromone, modulates the melanogenesis in a dose-dependent manner [29].

Ellagic acid, a polyphenol isolated from strawberries, green tea and geranium can be used effectively and safely in treating and preventing melasma and other UV-induced hyperpigmentation. Its mechanism of action is inhibition of the tyrosinase activity and proliferation of the melanocytes in a dose-dependent manner [29].

Another botanical extract, gentisic acid, which is derived from gentian roots, is an effective depigmenting agent particularly in alkyl ester form [29,64]. Studies have shown that this substance inhibits melanogenesis without cytotoxicity and mutagenesis [29].

Hydroxycoumarins are antioxidants and strongly inhibit the tyrosinase. They are natural lactones of phenyl propanoic acid with benzopyranone nucleus [29]. Umbelliferone or 7-hydroxycoumarin, is a phenolic compound of Apiaceae (Umbelliferae) family such as carrot and coriander. It has sun-blocking, antioxidant and anti-inflammatory properties [38].

Cinnamic acid, derivative of acidcassia and ginseng, is effective in the treatment of melasma via inhibiting the tyrosinase activity [20,38] and reducing the tyrosinase expression [29]. In a study, Tan et al. showed that in comparison with hydroquinone, this agent is more potent in inhibiting tyrosinase activity [86].

Some oral botanical therapies such as procyanidin, pycnogenol, polypodium, leucotomos extract and Chinese herbs are effective in the treatment of hyperpigmentation via their strong antioxidant properties [11]. Pycnogenol, a standardized extract obtained from the bark of the French maritime pine Pinus pinaster, is effective in treating melasma in oral form [29,38]. It has high bioavailability, synergistic action of its constituents and low incidence of side effects on oral intake [29,87]. It acts as antioxidant and anti-inflammatory agent [29,38]. Additionally, it plays a role in regenerating and protecting the vitamins C and E [29].

Other extracts such as Broussonetia kazwoki, B. papyrifera, Cornus officinalis, Rhus javanica and Pinus densiflora through inhibiting tyrosinase and DOPA oxidation in a dose-dependent manner are effective in treating melasma [29,38].

Polypodium leucotomos extract, derived from the tropical fern of Polypodiaceae family, has immune-modulatory, anti-oxidative and photo-protective properties. Because of these multiple mechanisms of action, in combination with a favorable side effect profile, this substance can be used in treating melasma [88].

Chemical Peels

Chemical peeling is controlled destruction of a part or of the entire epidermis, with or without the dermis by application of chemical agents to the skin. It is effective in treating melasma through removal of the unwanted melanin pigments. Generally, chemical peeling is used for the epidermal and mixed forms of melasma, because treating the deeper variants often increases the risk of complications like hypertrophic scarring and permanent depigmentation [31].

Chemical peels can be administered for treating melasma alone or in combination with other in-office procedures and topical creams to achieve synergistic effects [29]. To achieve optimum response, choosing an appropriate peeling agent with appropriate concentration and therapeutic sessions are all important [31]. Additionally, pretreatment with depigmenting agents as priming agents like tretinoin cream, hydroquinone cream and glycolic acid at low concentration, not only provides uniform penetration of peeling agents, but also by reduces the seborrhea and thinning the stratum corneum, accelerates the re-epithelialization, subsequently enhances healing and maintains the effects of the chemical peels [31,49]. Furthermore, these agents have lightening effect by enhancing dispersion of the melanin granules [49]. To achieve better results, this agent is better to be prescribed 2 weeks before initiating the peeling sessions [31,49]. In a single-blinded study, Garg et al. showed that administration of hydroquinone as priming agent compared to tretinoin had better results in enhancing the therapeutic response to glycolic acid peels in melasma and decreasing the risk of post peeling hyperpigmentation [49].

To treat melasma, superficial and medium depth chemical peels are used. Deeper peels are not appropriate for melasma; additionally, these deeper peels are associated with more complications such as hypo and hyperpigmentation, scarring, secondary infection, allergic reaction, acneiform eruption, persistent erythema and milia formation [29].

Alpha hydroxy, beta hydroxy and alpha keto peels have been used for treating resistant melasma [29]. Some of the most effective peels administered for the treatment of melasma include in:

Glycolic acid

It is the most commonly used alpha hydroxy peel, administered as a 30-70% solution [31]. It can be derived from sugarcane, sugar beets, pineapple, cantaloupe and unripe grapes [55]. In comparison with other alpha hydroxy acids used as chemical peels for treatment of melasma, glycolic acid is the safest and most versatile one because it has the smallest molecule and easily penetrates the epidermis [49]. It has successfully been used in treating the epidermal and mixed types of melasma, whereas the dermal types are almost resistant to this

treatment [31,49]. Its mechanism of action is through thinning of the stratum corneum and enhancing the epidemolysis [37].

Mild burning, erythema, desquamation and a transient PIH are reported side effects with this peel [31]. It can be an effective adjunct to topical treatment [28].

Lactic acid

This agent, classified in the group of alpha-hydroxy peels, has activities similar to glycolic acid. However, it has not been tried extensively for the treatment of melasma [31]. In a clinical trial, Sharquie et al. showed that lactic acid is a safe, effective and less costly peeling alternative for melasma, even in the patients with dark skin [89].

Phytic acid peel

It is an alpha hydroxy peel, requires a low PH for efficiency. This novel peel does not need neutralisation. Although there is no published work about its efficacy in the treatment of melasma, it appears that it can be administered for this pigmentary disorder [31].

Mandelic acid

It is an aromatic alpha-hydroxy acid, extracted from bitter almond, which has satisfactorily been used in treating in melasm, even in its dermal types [29]. Because of its large molecular weight and subsequently slow penetration into the skin, this agent is less irritating [29,31].

Salicylic acid

It is a beta hydroxy acid, which is safe and efficacious in the treatment of melasma [31,49,64]. It acts through the following mechanisms:

Anti-inflammatory activity [31].

Diffuse whitening effect [31,90].

It penetrates the skin quickly; hence, the risk of PIH is low with this agent [31].

Lipohydroxy acid

This salicylic acid derivative with an additional fatty acid chain, has increased lipophilicity and keratolytic effect [29,31]. In comparison with salicylic acid and glycolic acid, its penetration is less. Because its PH is close to physiologic skin PH, it makes no irritation and does not require any neutralization [29]. Though this agent has shown good results as peeling agent in treating acne, it is yet to be demonstrated if this is equally effective and safer than the conventional salicylic peels in patients with melasma too [31].

Salicylic mandelic acid peel

It is the combination of an alpha hydroxy acid (mandelic acid) and a betahydroxy acid (salicylic acid). Salicylic acid penetrates the skin quickly, whereas mandelic acid is slow in action; hence, it appears that the combination of these two agents would serve as an effective peeling for treating melasma. Yet no data about its efficacy in the treatment of melasma has been published [31].

Pyruvic acid

It is an alpha keto-acid, administered in treating melasma [29,31]. This agent in a concentration of 40% to 70% acts as a superficial peels [29]. Intense burning is the side effect reported in peeling with pyruvic acid which has limited its use [31].

Trichloroacetic acid peel

Although it is effective in the treatment of melasma, it is less frequently administered in the darker skin types due to high risk of complications in this group of patients. To achieve good response, low concentrations of this agent [10-35%] are preferred which reaches up to the upper papillary dermis; hence trichloroacetic acid peel is not appropriate for treating the dermal and mixed forms of melasma. Scarring, dyschromias, severe burning and cracking are reported side effects with this peel [31].

Jessner's solution

This is the combination of resorcinol, salicylic acid and lactic acid in ethanol, administered as a superficial peeling agent in treating melasma. It can be used in combination with other peeling agents like glycolic acid and trichloroacetic acid. It appears that combination of this solution with trichloroacetic acid results in more uniform penetration and an excellent peel with safe concentrations of the latter agent [31].

Tretinoin peel

It has successfully been used in the treatment of melasma [29,31]. It appears that its mechanism of action is similar to that of topical tretinoin, through changing the epidermis and dispersing the melanin pigments [31]. In a study, Khunger et al. showed that 1% tretinoin peel was as effective as 70% glycolic acid peel in the treatment of melasma with only minimal side effects [91].

Acidified amino acid peels

These peeling agents due to their potent antioxidants, tyrosinase inhibitory and exfoliant actions are effective in treating melasma. As they have hydration properties and their PH is close to physiological PH, they are well-tolerated, particularly in patients with dry and sensitive skin [29]. In comparison with glycolic acid, these peels have a better side effect profile, because these are less irritating [29,92].

Microdermabrasion and dermabrasion

With microdermabrasion, only the stratum corneum is removed without damaging to viable epidermis. This modality is effective and well tolerated in cutaneous hyperpigmentations. Yet it has not been tested specifically for treating melasma [37].

By dermabrasion, the skin down to the level of the upper or mid-dermis is abraded [37]. Its efficacy has been shown in treating melasma [6,47,32]; however, it is associated with an increased risk of PIH and other more serious adverse skin changes [37,32].

Light and laser therapy

Laser therapy for melasma based on the theory of selective photothermolysis proposed by Anderson and Parrish. According to this theory when a specific wavelength of energy is delivered in a time

duration shorter that the thermal relaxation time of the target chromophore, this energy is restricted to the target and causes less damage to the neighboring tissue [36]. This selective wavelength for targeting melanin is between 630 and 1100 nm [36,93]. In addition to wavelength, selecting an appropriate pulse width is important for targeting melanin. For selective destruction of the melanosomes, submicrosecond laser pulses [<1 μs] are required [36].

Generally, regarding their side effect profile and high cost, lasers and lights are the choice only for resistant melasma, especially in fair-skinned patients. The mechanism of lasers in treating melasma has histopathologically been proven to be through decreasing the number of melanocytes and eliminating the melanin in the surrounding keratinocytes [29]. Additionally, as the role of cutaneous blood vessels in the pathogenesis of melasma has been suggested, it appears that not only targeting the blood vessels along with the melanin pigment is effective in treating melasma, but also it leads to lower recurrence rate of melasma after the cessation of therapy [18,29]. In a study, Lee et al. showed the efficacy of copper bromide laser in the treatment of melasma through decreasing marker of vascularity [94].

Generally literature reviews have suggested that post inflammatory hyperpigmentation [36], rebound hyperpigmentation, relapse and darkening of melasma and unmasking of subclinical melasma are common complications with light and laser therapies [51,29]. It appears that destroying the pendulous cells during the laser therapy leading to their dropping into the dermis is responsible for heavy hyperpigmentation [18]. Additionally, damage to basal cell layer and release of archidonic acid, prostaglandins and leucotrienes resulting in stimulation of the epidermal melanocytes are another causes for post laser hyperpigmentation [36].

Intense pulse light (IPL), Q-switched neodymium-doped yttrium aluminum garnet (Nd:YAG; 1064nm), Q-switch alexandrite, Q-switched ruby [694 nm]2940-nm, Erbium:Yttrium-Aluminium-Garnet (Er:YAG), diode [840 nm], PDL [595 nm], non-ablative fractioned 1550- nm erbium (Er)-doped and ultra-pulsed CO_2 lasers will be used successfully for treatment of melasma [51,93]. Some of these modalities have be explained in the following:

IPL

The IPL has been approved by the Food and Drug Administration for the treatment of a variety of benign pigmentary and vascular lesions [95]. It is a broad-band light source that is highly effective in treating melasma through the following mechanisms.

Epidermal coagulation due to the photothermolysis secondary to light energy absorption by the melanin in the keratinocytes and melanocytes followed by micro-crust formation [36]

Effects on the vasculature [51]

Regarding its low side effect profile and its influences on a wide range of cutaneous structures, especially deeper structures, Zaleski et al. suggested that the IPL is an appropriate option for treating melasma, particularly its dermal and mixed types. Additionally, minimal preoperative preparation, easy application, minimal post-treatment care and lack of downtime are other advantage of this therapeutic modality [51].

It is better to initiate the treatment of melasma with 500-550 nm filters for epidermal lesions and higher wavelength filters for deeper lesions [36]. To acquire better response, repeated therapeutic sessions are needed. Although the addition of the Q-switched lasers to the IPL increase its efficacy, the risk of post-inflammatory hyperpigmentation is higher [51].

Q-switched Nd:YAG

The Q-switched Nd:YAG laser is effective in treating melasma via the following mechanisms

Induces sub-lethal injury to the melanosomes, leading to the fragmentation and rupture of the melanin granules.

Subcellular damage to the upper dermal vascular plexus.

Stimulating the formation of collagen resulting in brighter and tighter skin [36].

"Laser toning" or "laser facial" is a technique using large spot size (6-8 mm), low fluence (1.6-3.5 J/cm^2), multiple passed of Q- switched Nd:YAG laser (1064 nm), done every 1-2 weeks for several weeks [36]. Studies have shown that the topical triple combination creams before this technique improves its efficacy and decreases the rate of post inflammatory hyperpigmentation [36,96].

The Q-switched Nd:YAG laser has been used for treatment of melasma with temporary responses and frequent side effects including erythema, edema, mottled hypopigmentation, melasma recurrence, rebound hyperpigmentation [36,51], physical urticaria, acneiform eruption, petechiae, herpes simplex reactivation and whitening of fine hair. To prevent these side effects, it is suggested that this laser should not be used for too many (>6-10) or too frequent (every week) laser sessions [36]. Studies have shown that the low-fluence Q-switched Nd:YAG laser treatment, which selectively target the dermal melanosomes without producing inflammation or epidermal damage can be used in all skin phototypes [25].

Q Switched alexandrite laser

The Q-switched alexandrite laser (755 nm) is an appropriate modality for the treatment of facial mixed- type melasma. In a comparative clinical trial, Fabi et al. showed that both the low-fluence Q-switched Nd:YAG and low-fluence Q-switched alexandrite laser were equally effective for improving the moderate to severe facial melasma. No significant side effect was reported in this study [97].

Q Switched ruby Laser

Although in comparison with Q-switched Nd:YAG lasers, Q-Switched ruby laser (694 nm) is more selective for melanin [36], in practice the efficacy of this laser for treating melasma is still controversial [36,64]. Its mechanism of action in the treatment of melasma is similar to that of the Q-switched Nd:YAG laser [36].

Er:YAG laser

The Er:YAG laser (2940 nm) has been used successfully in the treatment of melasma, but its effectiveness is temporary [51, 96]. Its light is highly absorbed by water, resulting to ablating the skin with the minimal thermal damage with low risk of post-inflammatory hyperpigmentation [36].

PDL

The efficacy of PDL in the treatment of melasma is based on the theory that skin vascularization plays an important role in the

pathogenesis of melasma; hence, it appears that this laser by targeting the vascular component in melasma lesions decreases the melanocyte stimulation and subsequent relapses. The combination of topical triple combination creams with this laser increase its efficacy [36].

Fractional Lasers

Fractional lasers are the only laser that has been approved by the U.S. Food and Drug Administration for treatment of melasma [28]. In comparison with other lase modalities, the fractional lasers have more advantages [36,37]. With this modality, the recovery is faster and the risk of complications such as hyperpigmentation, hypopigmentation and scarring is low [36].

Studies have shown that in the comparison with the conventional triple-agent creams, the non-ablative fractioned 1550 nm Er-doped laser is more effective in early post-treatment phase, but their efficacies are equal after 6 months. It appears early satisfaction of laser therapy is secondary to the faster initial clearance and more effectiveness on dermal components of melasma [51]. Studies have confirmed the efficacy of fractional 1,927 nm thulium fiber laser in the treatment of melasma [98,99]. The wavelength of this laser possesses a high absorption coefficient for water, conferring greater ability to target epidermal processes such as dyschromia [99].

Although fractional lasers have shown initial promise, they can't produce sustained results [29]. Erythema, post-inflammatory hyperpigmentation, edema, burning sensation and pain are side effects of non-ablative fractioned 1550 nm laser [51].

Combination of lasers

To enhance the efficacy of lasers in treating melasma, their combination can be used [29]. In a study, Nouri et al. showed that the combination of pulsed CO_2 and Alexandrite lasers is highly effective in improving melasma. They explained that this significant response is due to the destruction of melanocytes by pulsed CO_2 and the elimination of dermal melanin by the alexandrite laser [100]. In other study, Wang and Liu showed the efficacy of the combination of Q switched Nd: YAG and alexandrite lasers in improving melasma [101].

The combination of lasers with topical depigmenting agents results in more significant and sustained responses in treating patients with melasma [29].

In an observational study on melasma patients, Kauvar showed that the combination of microdermabrasion and low-fluence Q Switched Nd:YAG laser is a simple, non-invasive procedure in treating refractory mixed-type melasma, with minimal side effects, no recovery time and long-lasting remission [102].

Therapeutic guideline

Therapeutic guidelines for melasma is summarized in Figure 1[103,104]:

Treatment assessment

The severity of melasma and its therapeutic response can be assessed subjectively, objectively, or semi-quantitatively [11].

Standard and UV light photography is a subjective method for evaluating melasma severity [11]. Serial photography is essential for assessing the response [50].

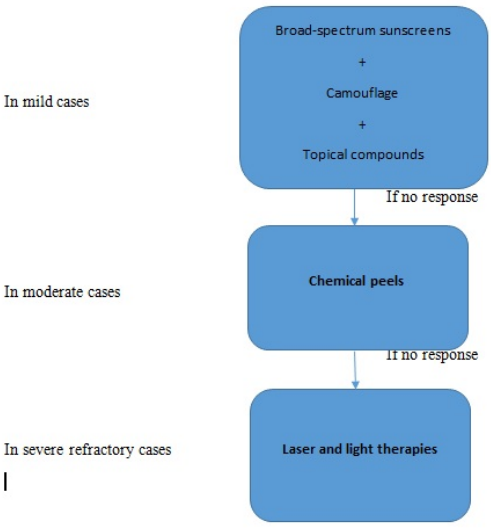

Figure 2: Therapeutic guideline for melasma.

Studies have shown that the Wood light examination is not precise in predicting response of melasma to treatment, because it is not accurate in determining the depth of melanin pigment [22].

Colorimetry and corneomelametry are objective measurements for assessing the melasma severity. In the colorimetry, which is the most commonly administered objective technique, pigments are analyzed based on wavelength of reflected light. In this technique, the skin color is assessed by the $L^*a^*b^*$ system in which L^* represents the black/white scale, a^* represents the red/green scale and b^* shows the yellow/blue scale. It appears that the colorimetry is able to detect changes in pigment density, not accurately measure changes in the melanin distribution. In, the corneomelametry, the melanin content of the stratum corneum is evaluated by histochemical analysis of skin-surface scrapings [11].

In vivo reflectance confocal microscopy (RCM) is a standard technique for assessing efficacy and safety of bleeching agents. In this method, pigmentary changes are detected at cellular levels [105].

Melasma Area Severity Index (MASI) scores is a semi-quantitative technique for assessing the therapeutic response [11]. This score assesses the severity of the melasma in each of the four regions including the forehead (30%), right malar region (30%), left malar region (30%) and chin (10%), based on three variables: percentage of the total area involved, darkness of the macules and homogeneity [37]. In a study, Pandya et al. showed that this score is a reliable for assessing the melasma severity [106]. The Physician's Global Assessment (PGA) is another scoring system used frequently for assessing outcomes of the treatment [37].

Zaleski et al. have shown that there is correlation between the severity of vascularity and melasma on the VISIA Complexion Analysis. This analysis is an easy method to determine which melasma are the best candidates for IPL therapy [51].

Dermoscopy has been used for assessing the area immediately after treatment sessions to choose the correct parameters for lasers and light

therapy; it appears that a transient hyperpigmentation (color change to grey) indicates a correct setting. The post light dermoscopic findings which are representative of clinical pictures of micro-crust formed during the process, can be classified into three patterns: [1] spotty/small dotted, [2] reticulated and [3] complex [clumped] [36].

Skin biopsy can be an appropriate option to detect the depth of pigment in melasma, but studies have shown that single skin biopsy may not be comprehensive because the lesions are heterogeneous in distribution of pigment [22,23]; hence, a reliable method for assessment is based on the epidermal/dermal melanin ratio covering the whole lesional skin [23].

Prognosis

Generally, melasma is difficult to treat, particularly in patients with darker skin [29]. The pigment of melasma develops gradually and similarly its resolution is also gradual [9]. Most of the melasma therapeutic modalities have their inherent side effects, especially on prolonged administration, have limited efficacy and relapses on discontinuation of therapy [29].

In the melasma treatment, a bimodal age response has been suggested; regarding this model, treatment response is better in patients younger than 35 years and older 45 years. It appears hormonal effects and increased incidence of dermal melasma in patients aged 35 to 45 are responsible for this bimodal response [51].

The traditional therapies are more effective for the epidermal type of melasma. They include sunscreen, bleaching agents, topical corticosteroids, tretinoin and chemical peelings [51].

An important problem associated with the treatment of melasma, particularly in ethnic skin is the high incidence of recurrence or relapse. Its incidence is high with the use of chemical peels because their mechanisms are through the temporary removal of cutaneous melanin without any effect on the melanogenesis or melanocytes [31].

Repigmention of melasma in most cases occurs probably secondary to persistent triggering factors [51]. On the other hand, the treatment should not be withheld simply because it has been shown that the source of the dermal pigment is the epidermis; hence, if the epidermal melanogenesis is inhibited for a long period, the dermal pigment will not be replaced and will be slowly removed [9].

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