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Melasma

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Abstract:

Melasma is a common aesthetic problem characterized by facial hyperpigmentation. It frequently affects young to middle-aged females who are Hispanic or of Asian, African or Middle Eastern descent. Its pathogenesis is still mysterious with multiple factors are being accused to play a role. Although many treatment options are currently available, melasma is difficult to cure with tendency to relapse.

Melasma (a term derived from the Greek word “melas” meaning black) is a worldwide prevalent acquired disorder of hyperpigmentation that commonly affects females with Fitzpatrick skin phototypes III-V (Goh and Dlova, 1999 and Gupta et al., 2006). It is characterized by appearance of symmetrical light to dark brown spots and patches on sun exposed areas mostly the face and especially the forehead, cheeks and chin (Kang and Ortonne, 2009). Melasma is sometimes termed chloasma (derived from the Greek word “chloas” meaning green) or mask of pregnancy when it develops in pregnant females (Handel et al., 2014a).

Historical aspects:

It was in the 18th century when the British surgeon and physician Daniel Turner referred to the presence of facial pigmentation. He described it as “There is a spot on the face. . .more peculiar, according to our great master Hippoc., to Big Belly’d women, and recon’d as one of the Signs of Conception.”(Turner, 1714). Daniel Turner acknowledged that Hippocrates attributed this facial pigmentation in pregnant females to the tanning effect of the ultraviolet radiations of the sunlight rather than being due to retention of the menstrual flux (Turner, 1726). Hypermelanosis affecting the face of some pregnant females is recognized by physicians of the present era as “melasma” (Sheth and Pandya, 2011a and Nicolaidou and Katsambas, 2014).

1 Classification of melasma:

Melasma can be classified into different types or patterns based on clinical examination, histological evaluation, Wood's lamp enhancement, dermoscopy or examination by confocal microscopy. There are three clinical patterns of melasma. The most common is the centrofacial pattern in which hyperpigmentation appears on the forehead, cheeks, nose, upper lip and chin. The malar pattern in which cheeks and nose are affected and the mandibular pattern where hypermelanosis occurs along the ramus of the mandible (figures 1-3) (Sanchez et al., 1981). Histologically, melasma is classified into three types (epidermal, dermal, and mixed) (Kang et al., 2002), that can be separated from each other using Wood's light examination. The lesions that enhance with Wood's light were described as epidermal, those that don't enhance were considered as dermal, whereas lesions with both enhancing and non-enhancing features are considered as mixed type. Some authors described a fourth type which is the Wood's light inapparent type in which patients have clinically apparent lesions with visible light examination but those lesions are unnoticed with Wood's light examination. This occurs in patients with skin phototype V and VI (Sanchez et al., 1981 and Asawanonda and Taylor, 1999).

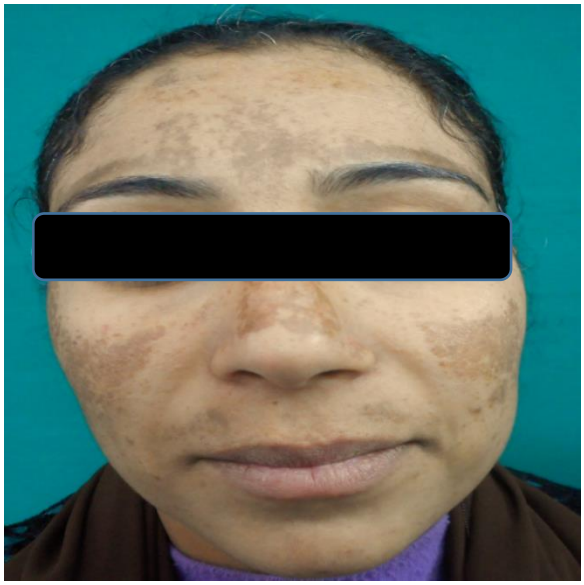

Figure (1): Centrofacial melisma

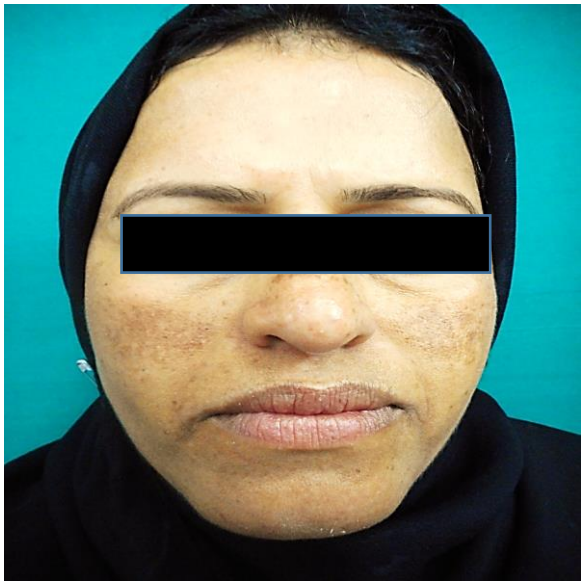

Figure (2): Malar pattern

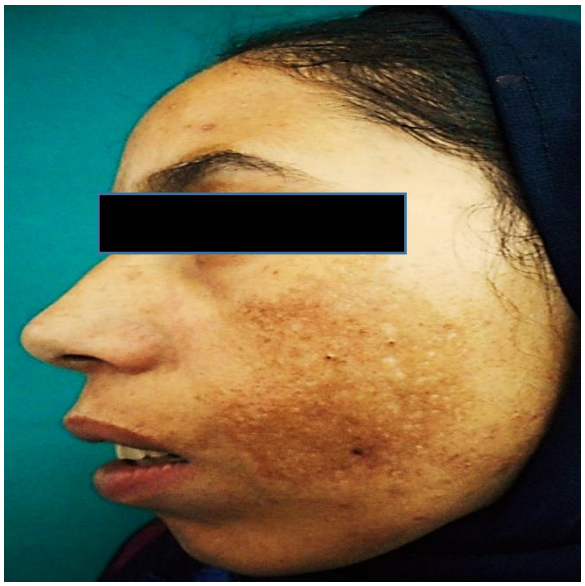

Figure (3): Mandibular pattern

Dermoscopy is a useful and appropriate objective tool that helps in classification of melasma lesions through visualization of their pigment component as well as their distribution through skin layers (Barcauí et al., 2009 and Manjunath et al., 2015). Reflectance confocal microscopy is a new tool used for non-invasive determination of the histological type of melasma. Recent studies revealed good concordance with histological analysis (Liu et al., 2011 and Costa et al., 2012).

2 Scoring index:

Melasma area severity index (MASI) was developed by Kimbrough-Green et al., 1994 for the assessment of melasma. The severity of the melasma in each of the four regions of the face (forehead, right malar region, left malar region and chin) is assessed based on three variables: percentage of the total area involved (A), darkness (D), and homogeneity (H). A numerical value assigned for the corresponding percentage area involved is as follows: 0=no involvement; 1=<10% involvement; 2=10-29% involvement; 3=30-49% involvement; 4=50-69% involvement; 5=70-89% involvement; and 6=90-100% involvement. The darkness of the melasma (D) is compared to the normal skin and graded on a scale of 0 to 4 as follows: 0=normal skin color without evidence of hyperpigmentation; 1=barely visible hyperpigmentation; 2=mild hyperpigmentation; 3=moderate hyperpigmentation; 4=severe hyperpigmentation. Homogeneity of the hyperpigmentation (H) is also graded on a scale of 0 to 4 as follows: 0=normal skin color without evidence of hyperpigmentation; 1=specks of involvement; 2=small patchy areas of involvement <1.5 cm diameter; 3=patches of involvement >2 cm diameter; 4=uniform skin involvement without any clear areas. To calculate the MASI score, the sum of the severity grade for darkness (D) and homogeneity (H) is multiplied by the numerical value of the areas (A) involved and by the percentages of the four facial areas (10-30%) (figure 4).

Total MASI score: Forehead 0.3 (D+H) A + right malar 0.3 (D+H) A + left malar 0.3 (D+H)A + chin 0.1 (D+H) A

In modified Melasma area severity index (mMASI), the severity of the melasma over the forehead, right malar region, left malar region and chin is assessed based on two variables: percentage of the total area involved (A), and darkness (D), the area involved and the darkness of the melasma are calculated as in MASI score (mentioned before). However homogeneity scoring is eliminated from the mMASI score as homogeneity assessement was found to be unreliable (Pandya et al., 2011). Total mMASI score: Forehead 0.3 (D) A + right malar 0.3 (D) A + left malar 0.3 (D) A + chin 0.1 (D) A

Hemi-Melasma Area and Severity Index score (hemi-MASI) was developed to obtain a right and a left MASI (Wang et al., 2014). Hemi -MASI score is calculated by assessment of the three key parameters of MASI; the area of involvement (A), darkness (D), and homogeneity of hyperpigmentation (H). The forehead (F) corresponds to 30% of the total face ;15% right (Rt), and 15% left (Lt), the Rt malar (m) region corresponds to 30%, the Lt malar region (m) represents 30% of the total face and the chin (c) corresponds to 10% of the total face (5% Rt, 5% Lt). The area of involvement (A) in each of these regions, darkness (D) and homogeneity (H) of pigmentation are rated on scales similar to MASI.

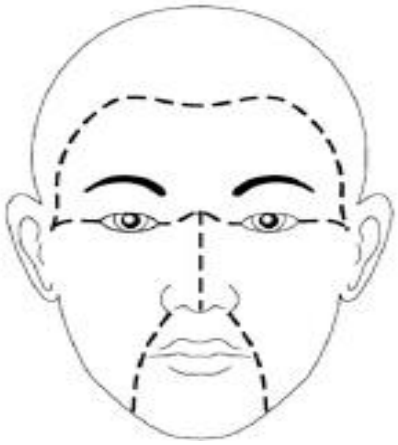

Figure (4): Total MASI score: Forehead 0.3 (*D+H*) *A* + right malar 0.3 (*D+H*) *A* + left malar 0.3 (*D+H*) *A* + chin 0.1 (*D+H*) *A (*Kimbrough-Green et al., 1994*)*

Calculation is done as follows for each side separately:

The Right-MASI equals: 0.15 (D + H) A Forehead + 0.3 (D + H) A Right malar + 0.05 (D + H) A Chin.

The Left-MASI equals: 0.15 (D + H) A Forehead + 0.3 (D + H) A Left malar + 0.05 (D + H) A Chin.

3 Epidemiology:

Although the exact prevalence of melasma in the general population is unknown, it varies widely among different studies from 1.5% to 33.0%. However, most of these studies were conducted on patients attending the dermatology clinics which may not indicate the prevalence in the overall population of the studied region reflecting some sampling bias (Werlinger et al., 2007 and Walker et al., 2008). A survey of Arab Americans living in the United States showed that melasma was the fifth most commonly self-reported skin disease representing 14.5% of the population surveyed (El-Essawi et al., 2007). Alternatively, a survey of 8008 rural inhabitants of Assuit governorate, upper Egypt, revealed melasma in 3.23% of the studied population (Abdel-Hafez et al., 2003).

There are some important correlations between melasma and clinical features including age, sex and skin phototype (Guinot et al., 2010; Perez et al., 2011 and Eleni, 2014). There is a strong correlation between melasma and the age of the patient. Some studies suggest that about 60% of the patients develop melasma before the age of thirty (Guinot et al., 2010 and Tamega et al., 2013). Melasma is 7- to 9-times fold more often in women than men (Eleni, 2014). The darker phototypes (Fitzpatrick skin types III-IV) are most prevalent in developing melasma throughout the patient's lifetime (Ortonne et al., 2009 and Perez et al., 2011).

4 Aetiology and risk factors:

Although the exact cause of melasma is still unclear, several factors are involved in its pathogenesis (Achar and Rathi, 2011). Understanding these factors will help better management of melasma patients, development of preventative measures and even predicting treatment outcomes and recurrence (Ortonne et al., 2009).

An important causative factor is the genetic predisposition, with 40% of the patients having at least one relative affected with the disease (Handel et al., 2014a). Other factors influencing and triggering the onset of melasma include exposure to UV radiation, darker skin colours (Guinot et al., 2010), hormonal changes during pregnancy, hormonal therapies, phototoxic drugs, cosmetics and anticonvulsant therapy (Khanna and Rasool, 2011 and Handel et al., 2014a). Anxiety traits and psychotropics are also closely related to the development of melasma (Handel et al., 2014b) raising the notion that melasma may be the mask of stress (Wolf et al., 1991).

All of these factors can enhance melanogenesis and increase the number of melanocytes; the essential histological abnormalities of melasma (Jadotte and Schwartz, 2010).

Familial and racial predisposition: Racial and/or familial predisposition indicates that genetic factors share in the development of melasma. Pigmentary disorders including melasma are more frequent among Hispanic and Asian racial groups with Fitzpatrick skin types III/V (Halder and Nootheti, 2003). Also, studies from different countries suggested the familial occurrence of the disorder. In Singapore, Goh and Dolva carried out a retrospective study on the epidemiology of 205 patients with melasma seen in a tertiary dermatological referral centre. They observed a positive family history of melasma in 21 (10.2%) patients (Goh and Dlova, 1999). In Iran, a study of the prevalence of melasma among pregnant females revealed a positive family history in 54.7% of the cases (Moin et al., 2006). Also, a study of the epidemiological characteristics of facial melasma in Brazilian women was conducted by Tamega et al. (2013) and they reported the familial occurrence of melasma in about 56.3% of the cases studied (Tamega et al., 2013).

Role of Ultraviolet irradiation in melasma: Melasma is often triggered or worsened by UV light exposure (Gupta et al.,

2006). Exposure to ultraviolet radiations is considered the most important provocative factor in the relapse of melasma and therefore, adherence to sun protection measures is strongly recommended. However, a lot of patients suffer from summer relapses of melasma inspite of using effective sunscreens (Passeron, 2013a).
UV exposure enhances melanin synthesis, melanocyte proliferation and migration. It also stimulates the expression of multiple cytokines, including alpha melanocyte stimulating hormone, and adrenocorticotropic hormone by keratinocytes, which further enhance melanogenesis and melanocyte proliferation (Im et al., 2002).

Visible light and melasma: Interestingly, visible light can produce an enhanced pigmentary response, at least in dark skin types (Passeron, 2013a). The effect of visible light on pigmentation was compared with that due to UVA exposure in the back of healthy volunteers. In dark skin patients (skin type IV–VI), both UVA and visible light can produce an increase in the skin pigmentation. Surprisingly this response was more intense and stable following visible light exposure as compared to UVA (Mahmoud et al., 2010). Accordingly, visible light can play a role in modulating the pigmentation process. However, based on these results, it cannot be deduced that visible light plays a role in melasma relapses, instead these results may explain the only partial protective effect of most sunscreens (Passeron, 2013a).

Drugs and melasma: The use of cosmetics, photosensitizing substances and intake of certain drugs are risk factors for developing melasma. A wide variety of chemicals such as arsenic, iron, copper, bismuth, silver, gold; and drugs such as antimalarials, tetracyclines, anticonvulsants, amiodarone, sulfonylureas, among others, can cause hyperpigmentation of the skin, by depositing in the surface layers or by stimulating melanogenesis (Handel et al., 2014a).

Stress and emotional factors: Some patients noted the onset of melasma following emotional stresses and affective disorders (e.g. depression) (Tamega et al., 2013). Propiomelanocortins (adrenocorticotrophic hormone and melanocyte stimulating hormone) are hormones linked to stress, and they are able to activate melanocortin receptors in melanocytes and stimulate melanogenesis. However, no available studies on states of anxiety among patients with melasma and healthy controls (Handel et al., 2014a).

The likelihood of presence of a neural element linked to melasma has been suggested. Bak et al. (2009) reported an increase in the number of keratinocytes expressing nerve growth factor receptor, neural endopeptidase and nerve fibers in the upper dermis of melasma skin. These findings reinforce the presumption that neuropeptides may play a role in the initiation or persistence of melasma (Bak et al., 2009).

Pregnancy and hormonal contraception: Melasma is related to female sex hormones as it often appears during pregnancy, and after the intake of oral contraceptive pills or hormone replacement therapy. However, the underlying etiopathological mechanisms are still unknown (Sheth and Pandya, 2011a).

Estrogen is involved in the development and/or maintenance of melasma (Varma et al., 2015). Mahmood et al.(2011) and Varma et al.(2015) found increased serum estradiol levels in various phases of menstrual cycles among melasma females as compared to age matched controls. Estradiol can up-regulate tyrosinase, tyrosinase-related protein (TRP)-1 and TRP-2 transcription in human melanocytes in vitro (Jian et al., 2011 and Kim et al., 2012). Additional studies showed increased expression of estrogen receptors in the lesional melasma skin (Lieberman and Moy, 2008 and Jang et al., 2010). Other hormones involved in the regulation of menstrual cycle including progesterone and **α-MSH (alpha melanocyte**

stimulating hormone) seem to play a role in the skin pigmentary disorders. In support, Jang and his colleagues reported that melasma skin is more progesterone-responsive than normal skin (Jang et al., 2010).

Further studies may lead to the development of topical antiestrogen therapies for melasma (Varma et al., 2015 and Natale et al., 2016).

5 Pathogenesis of melasma:

Melanin is the main pigment determining skin colour, and appropriate pigmentation guards skin cells against ultraviolet radiation. The synthesis of melanin is catalyzed by melanogenic enzymes, namely, tyrosinase. Tyrosinase catalyzes hydroxylation of L-tyrosine to L-DOPA, and subsequent oxidation to generate dopaquinone , tyrosinase-related protein-1 (Tyrp-1) and tyrosinase-related protein-2 (Tyrp-2) catalyze further reactions for melanin synthesis in a process termed as melanogenesis (Cichorek et al., 2013).

Melanogenesis in mammals is a complicated process that occurs within the melanosome, an organelle that contains pigment-producing enzymes; and the process is regulated by a number of factors, including hormones, differentiation factors, growth factors, and cytokines (Slominski et al., 2004 and Costin and Hearing, 2007).

Melasma is a disorder of the skin pigmentary system with enhanced melanogenesis being the base for the evolution of melasma. In support, in melasma skin, there is an increased expression of the tyrosinase enzyme (Kim et al., 2013a), tyrosinase related protein-1 (Kang et al., 2002), and tyrosinase related protein-2 (Kwon and Park, 2014).

The pathogenesis of melasma entails complex underlying genomic and proteomic basis together with other effectors such as alpha-melanocyte stimulating hormone (α-MSH), inducible nitric oxide synthase (iNOS) stem cell factor and c-kit, nerve growth factor receptor expression and vascular endothelial growth factor which are implicated in pigmentation (Ortonne and Bissett, 2008).

Melasma skin showed greater keratinocyte expression of α-MSH (Im et al., 2002) and inducible nitric oxide synthase (Jo et al., 2009) as compared to the adjacent skin, both involved in induction of melanin synthesis. Kang et al. (2006) reported increased expression of stem cell factors in dermal fibroblasts and c-kit in melasma lesional skin. Moreover, nerve growth factor receptor was found to be greater in keratinocytes of the lesional skin (Bak et al., 2009). The expression of vascular endothelial growth factor is increased in keratinocytes of melasma skin compared to adjacent healthy skin, in addtion functioning vasocoendothelial growth factors (VEGF) receptors were detected in human melanocytes in vitro. These notions has led to the presumption that VEGF affects the process of melanin synthesis in the skin (Kim et al., 2005 and Kim et al., 2007).

Furthermore, in melasma, there is up-regulation of genes regulating melanogenesis and Wnt signalling and down-regulation of genes involved in the lipid metabolism in melasma lesional skin as compared with normal surrounding one (Kang et al., 2011). For instance, *H19* gene and Wnt inhibitory factor-1 *(WIF-1)* are downregulated. Alternatively, PDZ domain protein kidney 1 *(PDZK1)* is upregulated in melasma lesional skin (Kim et al., 2010; Kim et al., 2012 and Kim et al., 2013b). Interestingly, the reduced transcription of *H19* in melanocyte–keratinocyte co-culture stimulates melanogenesis and increases the transfer of melanin to keratinocytes suggesting a role for *H19* in melasma development (Kim et al., 2010). It is worth mentioning that all of the abovementioned findings emphasize a crucial role for keratinocytes and not only melanocytes in the pathogenesis of melasma (Passeron, 2013a).

6 Pathological changes in melasma:

Histologically, melasma is classified into three types: epidermal, dermal, and mixed, defined clinically by Wood's lamp (Kang et al., 2002).

In epidermal melasma there is excess melanin in the basal, suprabasal, and may be throughout the epidermis up to stratum corneum. In the dermal variety, the upper and deep dermis are occupied with melanophages in the perivascular array. The mixed type has pigment deposition in the both epidermis and dermis (Kang et al., 2002 and Grimes et al., 2005).

Epidermal hyperpigmentation and basement membrane defect in melasma: The most important histologic hallmark of melasma is the presence of excess melanin in the epidermis. Fontana-Masson staining revealed that, the amount of melanin in melasma skin throughout all layers of the epidermis, including the stratum corneum, is greater than that in the surrounding normal skin (Kang et al., 2002; Hernández-Barrera et al., 2008 and Torres-Alvarez et al., 2011).

Kang and his colleagues examined the density of the melanocytes in melasma skin of 56 Fontana-Masson-stained histologic sections. Quantative image analysis revealed increased melanin content as well as density of melanocytes (Kang et al., 2002). Similarly, Lee et al., 2010 noted greater number of epidermal melanocytes in the melasma skin after Melan-A staining of biopsies obtained from the lesional skin compared to normal skin (Lee et al., 2010).

Ultrastructurally, both keratinocytes and melanocytes in melasma skin have greater number of mature melanosomes along with considerably greater number of dendrites per keratinocyte (Grimes et al., 2005 and Miot et al., 2010). There is an increased activity of melanocytes in melasma skin resulting from an increased number of organelles within the melanocytes of the lesional melasma skin as compared with the adjacent normal skin (Kang et al., 2002).

The presence of free melanin and melanophages in the dermis of melasma skin is due to basement membrane defect that permits the downfall of the melanin and the migration of melanocytes and melanin into the dermis (Kang et al., 2002 and Torres-Alvarez et al., 2011). Studies evaluated the status of the basement membrane in melasma skin reported variable results, for example Sanchez et al. reported that vacuolar degeneration of the basal cell keratinocytes and localized disruption of the basement membrane in 3.9% (3/76) of the melasma skin specimens (Sanchez et al., 1981).

The presence of pendulous melanocytes together with disruption of the integrity of the basement are distinctive features of melasma (Lee et al., 2012). Another study on melasma patients with Fitzpatrick skin types IV and V using D-PAS staining and anti-collagen type IV immunohistochemistry revealed basement membrane defects in 95.5% and 83% of the skin specimens, respectively (Torres-Alvarez et al., 2011). This basement membrane damage could be the result of increased levels of matrix metalloproteinase (MMP)-2 and MMP-9, with breakdown of type IV collagen and type VI collagen in the skin due to chronic UV exposure (Inomata et al., 2003). In normal skin, cadherin 11(CDH11) is expressed mainly in dermal fibroblasts and, to a lesser extent, in keratinocytes, but not in melanocytes. In melasma skin CDH11 is over expressed by fibroblasts and keratinocytes. CDH11 induces expression of N-cadherin in dermal fibroblasts and keratinocytes and increases melanogenesis through cell–cell adhesion between fibroblasts or keratinocytes and melanocytes via N-cadherin which should be accompanied by disruption of the basement membrane and migration of fibroblasts through the basement membrane. To achieve this, CDH11 induces basement membrane damage by increasing the expression of MMP-1 and MMP-2 in fibroblasts and MMP-1 and MMP-9 in keratinocytes (Kim et al., 2016 and Kim et al., 2014).

Dermal changes in melasma: Several studies indicate the involvement of dermal alterations in the development of melasma (Kang et al., 2006; Kim et al., 2007 and Kang and Ortonne, 2009).

Fibroblasts and solar elastosis: In melasma skin there is an increased production of stem cell factor from fibroblast together with overexpression of c-kit (Kim et al., 2007). Moreover, increased production of fibroblast derived cytokines stimulate melanin synthesis and melanocytes replication in culture (Suzuki et al., 2002). Solar elastosis is a common histologic finding in melasma skin. Kang et al., (2002) noted a moderate-to severe degree of solar elastosis in 93% of the melasma patients .This degree of solar elastosis was significantly higher in the diseased skin than in the surrounding perilesional skin (83% vs. 29%) (Torres-Alvarez et al., 2011). Moreover, thick, highly curled, and more fragmented elastic fibers were found in melasma skin in Verhoeff-van Gieson-stained sections (Kang et al., 2002).

Increased vascularization: There is an increasing evidence both clinically and histologically that the number of blood vessels is greater among melasma lesions than in the surrounding normal skin (Kim et al., 2007 and Kang et al., 2010 and Passeron, 2013b). In support, an immunohistochemical study using antibodies against factor VIIIa-related antigen revealed an increased dermal vascularity with significantly higher number of dilated dermal blood vessels, in melasma skin as compared to adjacent normal skin (Kim et al., 2007). These findings are supported by laser confocal microscopy examination (Kang et al., 2010). The precise role of the vascularization in the development of the hyperpigmentation in melasma is still unclear (Passeron, 2013a).

Mast cells: Mast cells are more prevalent in melasma skin than in non-lesional skin, particularly within elastotic areas among the dermis (Na et al., 2013). Using an antitryptase antibody, the number of mast cells was statistically significantly high (58 ± 39.9 cells/mm^2) in melasma skin as compared to the perilesional skin (37 ± 28.8 cells/mm2) , (p<0.04) (Torres-Alvarez et al., 2011). The role of the mast cells in the development of melasma is still to be clarified (Kwon and Park, 2014). Similarly, there is a mild lymphohistiocytic infiltrate in melasma skin (Grimes et al., 2005).

Taken together, melasma represent a complex disorder being not limited to altered melanocytes. Instead, melasma results from a complex network of cellular cross-talks between keratinocytes, fibroblasts, blood vessels and melanocytes (Kang and Ortonne, 2009) and (Passeron, 2013a).

7 Treatment of melasma:

Melasma can significantly affects the individual's quality of life and sense of well-being (Freitag et al., 2008) and (Passeron, 2013a). Accordingly, its management is not only challenging with inconsistent and unpredictable outcomes but is also associated with frequent relapses. Therefore, an ideal modality for treatment of melasma is still beyond physicians' reach (Sarkar et al., 2012a). During treatment of melasma both depigmentation and protection from sunlight are targeted (Shankar et al., 2014).

The treatment options in melasma include sunscreens, topical depigmenting agents, chemical peels and lasers. Alternative therapeutic modalities include less-tried systemic agents such as fish oil, green tea and deoxyarbutin (Victor et al., 2004; Azzam et al., 2009 and Sheth and Pandya, 2011b). To date, there is no single agent with established efficacy among all melasma patients, therefore two or three agents are used simultaneously. In spite of this wide range of therapeutic options, treatment of melasma remains a challenge, and many patients may show only a mild to moderate improvement (Sarkar et al., 2012a).

Sunscreens: The regular use of broad spectrum sunscreens is essential to prevent exacerbation or recurrence of melasma (Shankar et al., 2014), because both visible and UV light can enhance melanogenesis in all skin types (Mahmoud et al., 2010). The use of combined physical and chemical blockers is important in the treatment of melasma (Sheth and Pandya, 2011b).The opaque sunscreens (e.g. titanium dioxide or zinc oxide) are effective in the protection against visible light (Castanedo-Cazares et al., 2014).

Topical depigmenting agents: Topical pigment reducing agents are chemicals that interfere with synthesis of melanin at different steps along the pathway of melanogensis. This includes:Inhibition of melanocytes' proliferation, inhibition of melanin synthesis and formation of melanosomes, and stimulation of breakdown of melanosomes (Rigopoulos et al., 2007). A summary of mechanism of action of different hypopigmenting agents is shown in Table (1).

Table (1): Classification of depigmenting agents and their mechanism of action (Shankar et al., 2014).

	Mechanisms of action	**Active molecules**
Before melanin synthesis	Tyrosinase transcription	Tretinoin, c-2 ceramide
	Tyrosinase glycosylation	PaSSO3Ca
	Inhibition of plasmin	Tranexamic acid
During melanin synthesis	Tyrosinase inhibition	Hydroquinone, mequinol, azelaic acid, kojic acid, arbutin, deoxyarbutin, Licorice extract, rucinol, 2,5-dimethyl-4-hydroxy-3(2H) furanone, N acetyl-glucosamine, resveratrol, oxyresveratrol, ellagic acid, methyl gentisate, 4-hydroxyanisole
	Peroxidase inhibition	Phenolic compounds
	Reactive oxygen species scavengers	Ascorbic acid, ascorbic acid palmitate, thiotic acid, hydrocumarins
After melanin synthesis	Tyrosinase degradation	Linoleic acid, a-linoleic acid
	Inhibition of melanosome transfer	Niacinamide, serine protease inhibitors, retinoids, lecithins, neoglycoproteins, soybean trypsin inhibitor
		Lactic acid, glycolic acid, linoleic acid, retinoic acid

	Skin turnover acceleration	Corticosteroids, glabiridin
	Regulation of melanocyte environment	Kojic acid, ascorbic acid
	Interaction with copper	Arbutin and deoxyarbutin
	Inhibition of melanosome maturation	Soybean trypsin inhibitor
	Inhibition of protease activated receptor 2	

PaSSO3Ca: Calcium pantetheine-S-sulfonate

***Hydroquinone (1, 4-dihydroxybenzene)*:** For more than 50 years, hydroquinone (HQ) has been well known as a topical agent for treatment of hyperpigmentation. Its efficacy in the treatment of melasma both when used alone or combined with other agents is well established (Draelos, 2007). HQ is a hydroxyphenol that is structurally similar to tyrosine. It acts through prevention of oxidation of tyrosine into dihydroxyphenylalanine through competitive inhibition of tyrosinase enzyme and thus melanin synthesis is prevented (Gillbro and Olsson, 2011).

The most common adverse reactions of HQ include mild skin irritation with erythema, itching, burning, stinging and allergic contact dermatitis. These effects can develop with the use of 4% rather than 2% concentrations of hydroquinone. Exogenous ochranosis can occur with the prolonged use of high concentration of hydroquinone (Zawar and Mhaskar, 2004 and Desai, 2014).

Corticosteroids: The mechanism by which topical corticosteroids produce pigment reducing effects on the skin is poorly defined (Bandyopadhyay, 2009). Several chemical mediators affect melanocytes such as prostaglandins and leukotrienes and thus the effects of corticosteroids on melanin synthesis are through their inhibitory effects on the production of these mediators (Gupta et al., 2006).

Topical corticosteroids can be used alone or in combination with other topical products. The side effects of the corticosteroids preclude their use as single agents in treatment of melasma (Gupta et al., 2006 and Bandyopadhyay, 2009). A combination therapy of topical corticosteroids together with other topical therapies has beneficial synergistic pigment reducing effects. It also decreases the possible skin irritation from other topical products such as tretnion. The side effects of topical corticosteroids include steroid induced rosacea, telangiectasia, hypertrichosis and perioral dermatitis (Bandyopadhyay, 2009).

Topical retinoids: the use of topical retinoids either alone or in combination with other topical hypopigmenting agents is well known in the treatment of melasma. Although the mechanisms underlying the lightening effect of retinoids are not fully understood (Ortonne, 2006), several mechanisms have been suggested including enhancement of epidermal cell turnover (Kasraee et al., 2003). Other possible mechanisms include decreasing melanosome transfer, interfering with transcription of tyrosinase, facilitating the penetration of other topical agents (Cestari et al., 2009), and potentiating the cytotoxic effect of skin

lightening agents on melanocytes through supressing the detoxification of toxic species (Ortonne, 2006).

Of note, when topical retiniods are used alone in treatment of melasma, the response is not observed until 24 weeks after the starting of therapy (Fisk et al., 2014). The most common adverse effect of topical retinoids is retinoid dermatitis with the occurrence of stinging, burning, redness, scaling , and dryness (Sarkar et al., 2013).

Triple Combination therapy: To date the most beneficial first line treatment in melasma is the triple combination regimen representing a combination of hydroquinone 5%, retinoic acid 0.1%, and corticosteroid 0.1%. This regimen was first suggested by Kligman and Willis aiming at providing synergistic effect of the three topical agents, reducing the duration of therapy, and decreasing the untoward effects of one another (Rendon et al., 2006). Some modifications of this formula is widely used in the treatment of melasma all over the world (Kligman and Willis, 1975). Tretinoin prevents the oxidation of HQ, enhances its cutaneous penetration and reduces steroid induced skin atrophy. Topical corticosteroids minimize skin irritation from both retinoids and HQ. Significantly, pigment reducing effects are attained by the synergistic actions of the triple combination than with applying each separate agent alone. A response to this combination therapy is noted within 8 weeks without considerable side effects (Sehgal et al., 2011).

Kojic acid: Kojic acid (5-hydroxy-2-hydroxymethyl-4-pyrone) is used as an alternative agent to hydroquinone in patients intolerant to hydroquinone. Kojic acid supresses tyrosinase activity by chelation of copper at the active site of the enzyme. It is available at concentrations ranging from 1% to 4% and also combined with hydroquinone. It should be used with caution as kojic acid can cause contact dermatitis (Draelos, 2007).

Azelaic Acid: Acts by inhibition of tyrosinase and mitochondrial enzymes. It has a selective cytotoxic effects on the abnormal melanocytes with minor effects on normally pigmented skin (Halder and Richards, 2004 and Gillbro and Olsson, 2011). A double-blind randomized study found that azelaic acid at 20% concentration was equally effective to 4% HQ in treatment of melasma but without its adverse effects (Baliña and Graupe, 1991). Azelaic acid can be prescribed in patients intolerant to hydroquinone (Shankar et al., 2014).

Chemical peels: Chemical peeling is a procedure in which application of a chemical solution to the skin is done in order to induce a controlled damage of a part or of the whole epidermis, with or without involvement of the dermis. This leads to exfoliation of the superficial lesions, followed by renewal of the epidermal and dermal tissues (Khunger, 2008).

Treatment of melasma using chemical peels is well-known. Useful peeling agents in treatment of melasma are used either alone or in conjunction with other topical depigmenting agents (Sarkar et al., 2012a).

Superficial and medium-depth peels have been are used in treatment of melasma with variable success, mainly in fair skinned patients (Sarkar et al., 2002 and Rendon et al., 2010).However caution must be taken on using chemical peels in patients with darker skin as the therapeutic outcomes are usually unacceptable with higher risk of post inflammatory hyperpigmentation or exacerbation of melasma itself (Grimes 2012a).

Chemical peels work through getting rid of melanin, rather than suppression of melanogenesis (Gupta et al., 2006). They also promote penetration, and hence, improve the efficacy of topical hypopigmenting agents when used together (Sarkar et al., 2012b).

The greater the depth of peeling, the higher the risk of complications. The use of superficial peels carries the lowest incidence of side effects, but is still accompanied by hyperpigmentation and post-peel erythema. The use of deeper peels carries higher risk of complications such as hypertrophic scarring and

permanent depigmentation (Sarkar et al., 2012a).

***Alpha hydroxy peels*:** Glycolic acid (GA) peels are the most frequently used alpha-hydroxy peel. They are used at concentrations of 30-70% GA solution. The mechanism of action of glycolic acid peels depends on accelerating shedding of melanised keratinocytes, resulting in melanin pigment loss and hastening skin turnover (Briganti et al., 2003 and Cestari et al., 2009). Studies using GA in treatment of melasma in ethnic skin showed a fair degree of improvement in nearly one-half of the patients (Lim and Tham, 1997; Javaheri et al., 2001; Grover and Reddu, 2003 and Godse and Sakhia, 2011). The patients having epidermal melasma showed the best results, followed by those with the mixed type, while those with the dermal variant were almost refractory to the effect of chemical peels (Grover and Reddu, 2003). The side effects associated with the use of GA peels include mild burning, redness, desquamation and a transient post inflammatory hyperpigmentation (PIH) (Sarkar et al., 2002).

Lactic acid is an alpha-hydroxy acid having actions similar to GA. It has not been used widely as a peeling agent in the treatment of melasma, although it is inexpenssive and readily available agent. Sharquie et al. (2005), reported that lactic acid peels is a safe and lactic acid is a useful peeling agent for treatment of melasma in dark skinned individuals. In their study, 20 patients were treated with 92% pure lactic acid for a maximum of six sessions, and a significant improvement was noticed in all the 12 patients who completed the study .

Beta hydroxy peels: Salicylic acid is a beta-hydroxy acid classicaly used in the treatment of acne. Its use in pigmentary disorders such as melasma has been tried with favourable results (Ejaz et al., 2008 and Kodali et al., 2010). Its ethanol solutions are an excellent peeling agent for many conditions in dark-skinned individuals such as acne, melasma and post-inflammatory hyperpigmentation (PIH) (Grimes, 2012b). As salicylic acid has anti-inflammatory properties it can reduce the PIH which usually follows the use of peeling agents on the skin (Sarkar et al., 2012a).

Trichloroacetic acid peel: Although trichloroacetic acid (TCA) peel is frequently used in fair skin, it is a less commonly favoured agent in darker skin types due to the greater incidence of post-peel hyperpigmentation (Grimes, 2012a). Application of TCA to the skin causes precipitation of proteins and coagulative necrosis of cells in the epidermis. In a comparative study on 40 Indian women, the overall fall in melasma area and severity index (MASI) after six TCA peels was comparable to that observed with a similar number of 10-35% GA peels. However, the TCA group complained of more severe burning as compared to GA. Also, post-peel crackening was seen in 35% patients in the TCA group and in none of the GA group (Kumari and Thappa, 2010). Another comparative study used different concentrations of TCA peels (TCA 20%, TCA 25%, and TCA 30%) and there was a significant reduction of MASI score from baseline. The use of 25%TCA was better in terms of both efficacy and tolerability whereas higher concentration (TCA 30%) was associated with higher incidence of side effects such as local irritations and postinflammatory hyperpigmentation (Moubasher et al., 2014).

Taken as a whole, TCA peels have comparable efficacy to GA peels in the treatment of melasma (Sarkar et al., 2012a), with 25% TCA being the most effective safe concentration (Moubasher et al., 2014). Caution must be taken while using them in dark skin due to a higher risk of adverse effects (Sarkar et al., 2012a).

***Jessner's solution*:** The combination regimen of resorcinol, salicylic acid and lactic acid in ethanol is widely used alone or in combination with other peeling agents owing to its high efficacy and good tolerability. Jessner's solution has intense keratolytic activity, initially causing loss of corneocyte cohesion within the stratum corneum and subsequently creating

intercellular and intracellular edema within the upper epidermis (Grimes, 2012c). In a comparative study, 20 female patients with melasma were treated either by a combination of modified Jessner'ssolution with 15% TCA on one side, or with 15%TCA alone applied to the other side. There was a better improvement on the side of the combination peel (Safoury et al., 2009).

Tretinoin peels, the mechanism of action of tretinoin peels is similar to that of topical tretinoin, i.e. via inducing epidermal changes with dispersion of melanin (Gupta et al., 2006).

Khunges et al. (2004) conducted a split face study of 10 Indian women, with1% retinoic acid peel applied to one side of the face while the other side was treated with 70% glycolic acid solution; every week for 12 weeks. There was a significant reduction in MASI on both sides, but without statistical difference between the two sides (Khunger et al., 2004).

To conclude, the traditional glycolic peels represents the gold standard chemical peel both in terms of safety and efficacy in the treatment of melasma. Lactic acid peels are less costly and have shown equivalent favourable results. The TCA peels are effective however, it can produce post inflammatory hyperpigmentation in dark skinned patients. The choice of peeling agent, the peel concentration as well as the frequency and duration between peels are all crucial to obtain the best results (Sarkar et al., 2012a).

Laser and light therapy: The role of laser in the treatment of melasma is limited. Some studies reported variable success with the use of Q-switched lasers (Wu et al., 2012), fractional lasers (Rokhsar and Fitzpatrick, 2005; Tannous and Astner, 2005; Naito, 2007; Goldberg et al., 2008; Trelles et al., 2010 and Goel et al., 2011), Intense pulsed light (IPL) (Wang et al., 2004), and combination lasers (Nouri et al., 1999; Angsuwarangsee and Polnikorn, 2003 and Na et al., 2012). The response to laser treatment is variable and inconsistent with frequent recurrences and high incidence of complications. For these reasons, in addition to the relatively high cost of laser sessions, lasers are not routinely recommended as the first treatment option in melasma. It is usually regarded as the last resort in selected refractory cases (Shankar et al., 2014).

Q-switched lasers, the absorption spectrum of melanin is broad throughout the visible light and near infrared regions. Q-switched lasers selectively destroy melanosomes by delivery of pulse energy in a nanosecond duration that is less than the thermal relaxation time of the melanosomes (50 to 500 ns) (Anderson and Parrish, 1983; Rox Anderson et al., 1989 and Arora et al., 2012).

Q Switched Nd:YAG Laser (QS Nd:YAG), is the most commonly used laser for the treatment of melasma (Arora et al., 2012).The 1064 nm QS Nd:YAG is well absorbed by melanin and due to its long wavelength it only causes minimal damage to the epidermis and is not absorbed by haemoglobin. The deeper skin penetration is also helpful to target dermal melanin. Low-dose QS Nd:YAG laser induces sublethal injury to the melanosomes causing fragmentation and rupture of melanin granules into the cytoplasm (Anderson and Parrish, 1983 ; Lee, 2003 and Bagherani et al., 2015). This effect is highly selective for melanosomes as this wavelength is well absorbed by melanin relative to other structures. There is also subcellular damage to the upper dermal vascular plexus which is one of the pathogenetic factors in melasma (Kim et al., 2007 and Bagherani et al., 2015).

Several studies evaluated the efficacy of QS Nd:YAG and they showed variable results. A split face randomized study enrolled 22 Asian melasma patients comparing the combination of 1064 nm QS Nd:YAG laser (for five sessions at 1-week interval) and 2% hydroquinone on one side with hydroquinone alone applied to the other side. There was a significant improvement on the laser side, suggesting that 1064 QS Nd:YAG laser is a useful treatment modality for

melasma (Wattanakrai et al., 2010). However, some studies used QS Nd:YAG laser for treatment of melasma with unsatisfactory results with only mild improvement noted in a limited number of patients (Xi et al., 2011 and Moubasher et al., 2014).

Also, side effects such as hypopigmentation and rebound hyperpigmentation together with recurrence of melasma were reported in a significant number of patients (Wattanakrai et al., 2010 and Moubasher et al., 2014).

Q Switched alexandrite laser (QSAL), wavelength 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 (Fabi et al., 2014).

Q Switched Ruby Laser (QSRL), The role of QSRL in treatment of melasma is still debatable (Picardo and Carrera, 2007). Some studies indicated that QSRL can only provide a slightly better treatment outcomes in treating melasma than the QS Nd:YAG laser (Tse et al., 1994). Alternatively, another study showed that QSRL is ineffective in treatment of melasma (Taylor and Anderson, 1994).

Erbium: *Yag Laser,* emits light with a 2940-nm wavelength that is highly absorbed by water-containing tissue. This feature allows the laser to vaporize away skin layers with negligible thermal damage, and thereby the risks of PIH is reduced (Manaloto and Alster, 1999).There are few studies available about the use of erbium:YAG in treating melasma (Arora et al., 2012).

Manaloto and Alster evaluated the effect of erbium:YAG laser in 10 female patients with refractory melasma. Although they found marked improvement immediately following laser treatments, this was associated with transient post-inflammatory hyperpigmentation. As such, the use of this laser is preserved only for refractory cases of melasma (Manaloto and Alster, 1999). Another study included fifteen Egyptian female patients with refractory melasma with full-face skin resurfacing using an erbium:YAG laser was performed and the results revealed that erbium:YAG laser resurfacing had effectively improved melasma in these patients; with the universal appearance of transient postinflammatory hyperpigmentation (Attwa et al., 2015). Also, The short-pulsed deep Er:YAG laser was found to effectively reduce epidermal type melasma, with a recurrence upon discontinuation of treatment (Wanitphakdeedecha et al., 2009).

Fractional lasers, the fractional photothermolysis can achieve skin resurfacing through production of multiple microscopic zones of thermal damage (microthermal zones, MTZ) together with extrusion of microscopic epidermal necrotic debris (MEND) including melanin, the use of fractional lasers (fraxel laser 1550nm) not only ameliorates the complications of the traditional ablative lasers such as hyper or hypopigmentation and scarring, but also hastens the recovery. Also, the use of this technique allows safe deeper penetration of skin layers and thus dermal melasma can be targeted (Manstein et al., 2004; Laubach et al., 2006; Rahman et al., 2006 and Katz et al., 2010).

Several studies reported favourable results and variable improvements with the use of fractional laser in treating melasma (Rokhsar and Fitzpatrick, 2005; Tannous and Astner, 2005 and Katz et al., 2010).

Intense pulsed light, is a non-coherent light source with a wide emission spectrum (500-1200 nm) and millisecond pulse durations (Fabi and Mitchel, 2012).

Previous studies showed that IPL is effective in the treatment of epidermal melasma (Arias and Ferrando, 2001),. Higher wave length filters and higher fluencies are more suitable in targeting deeper melanin in dermal or mixed melasma. However caution should be taken

when treating dark skinned patients as higher fluencies can cause PIH (Arora et al., 2012).

Combination of lasers, the use of combination of ablative and pigment selective lasers in treating melasma has been tried. The idea is to eliminate excess melanin and abnormal melanocytes in the epidermis by the action of the ablative laser and then to destroy dermal melanophages using Q switched pigment selective laser. A study compared combined ultra-pulse CO_2 laser and QS alexandrite laser (QSAL) on one side with the use of QS alexandrite laser (QSAL) alone. The side treated by the combination treatment showed better response compared to the side that received QSAL alone (Angsuwarangsee and Polnikorn, 2003).

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