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Review Article

RECENT ADVANCES IN THE TREATMENT OF MELASMA: A COMPREHENSIVE LITERATURE REVIEW

Shruti Kayastha*, Vibhav Lal, Prem Kapuri and Prof. Dr. Sun Yi

Dermatology department, Jingzhou central hospital, Yangzte university, Jingzhou, Hubei province, China

ABSTRACT

Background: Many studies on the treatment of melasma have been published in the past decades, including retrospective and prospective case series, case reports and multicenter survey reviews. However, there have been new progresses in the treatment of melasma, aside from those that are currently being implemented in the hospitals. This paper will present new topical, oral and procedural therapies culled from different studies done from the past five years based on successful treatments.

Objectives: This review will provide an up-to-date discussion the current literature on melasma, including clinical diagnosis, pathogenesis, histology, and treatments including a presentation of new topical, oral, and procedural therapies. This article is a comprehensive literature review on previously conducted studies and does not involve new studies of human or animal subjects performed by the authors.

Methods: A search on PubMed/Medline was performed for clinical studies the latest therapies involved in the management of melasma in terms of topical, oral and procedural types. Similar articles with varying results of success were grouped together and divided into those three different types of therapies available for melasma.

Results: Twenty studies, published from 2013 through 2019, were analyzed by the researcher representing around 1254 treated patients. The number of patients treated according to type of therapy were as follows: oral (n = 781), topical (n = 1083), and procedural (n = 284). The types of treatment had overlaps depending on the patients' needs, so some of them had oral and topical while others had oral and procedural. The recent advances in the three types of therapies are discussed here in this study.

Conclusions: The recent therapies in treating melasma has been grouped into three – for purposes of discussion in this study – topical, oral and procedural. For new topical treatments, the following therapies were discussed - pigment-correcting serum, methimazole, flutamide, and cysteamine.

Key Words: melasma; pigment-correcting serum, flutamide, cysteamine, methimazole

INTRODUCTION

Melasma is a pigmentation disorder, an acquired hypermelanosis of sun-exposed areas in three predominant facial patterns: centrofacial, malar, and mandibular (Sanchez, et al., 1981). It comes out in symmetrically distributed hyperpigmented macules and is either mottled or coalescent. Its most common locations are those areas of the skin that receive the most sun exposure, usually at an excessive amount. In terms of its morphology, it can be seen as symmetric reticulated hyperpigmented patches with irregular borders on the centrofacial region, malar cheeks, mandible, and on rare occasions – the upper chest and extremities.

The major clinical pattern in 50–80% of cases is the centrofacial pattern (Tamega Ade, et al., 2013) which includes the forehead, the nose, the chin, the cheeks, and the upper lip. It can also occur in other areas of the body that gets sun exposure (Lyford, 2018). In fact, a newer pattern called extra-facial melasma has affected patients on their non-facial body parts, like the upper extremities, the sternum, the neck and forearms (Ritter, et al., 2013). The mandibular melasma is present on the jawline and chin. The malar pattern which is restricted to the malar cheeks on the face affects older individuals and may be mostly related to severe photodamage (Mandry Pagan, & Sanchez, 2000). It is also most common among Asian women in their 30s and 40s (Newcomer, et al., 1961) and those with darker skin types. However, it can still occur in all skin types (Hexsel, et al., 2014). The most commonly believed causes are chronic ultraviolet (UV) exposure,

genetic factors, and sex hormones as evidenced from epidemiologic studies (Ortonne, et al., 2009).

Figure 1: Asian women between the ages of 30 and 40 are the most prone to have melasma

Even though this disease is relatively common, its management has remained challenging given the incomplete understanding of the pathogenesis, its chronicity, and recurrence rates. This article will present traditional treatments for melasma, as well as promising new treatments, including topical, oral, and procedural therapies. As mentioned earlier the pathogenesis of melasma has till now been fully expounded but the pathogenic mechanisms involved are believed to be heterogeneous in different individuals and ethnic groups. Most commonly involved mechanisms for altered skin pigmentation, is UV-induced pigmentation. No doubt, an increase in keratinocyte-derived melanogenic factors and their receptors occur in both UV-induced melanogenesis and melasma. Increased expression of female sex hormone receptors and the identification of the PDZ domain containing 1 (PDZK1) signaling mechanism provide insights to further our understanding of melasma. In addition to keratinocyte-derived paracrine factors, the role of paracrine factors from dermal fibroblasts, such as stem cell factor (SCF) and Wnt inhibitory factor-1 (WIF-1), is elucidated in melasma. Furthermore, the involvement of ion exchangers and microRNAs (miRNAs), such as H19 miRNA (miR-675), are also suggested (Lee, A-Y., 2014).

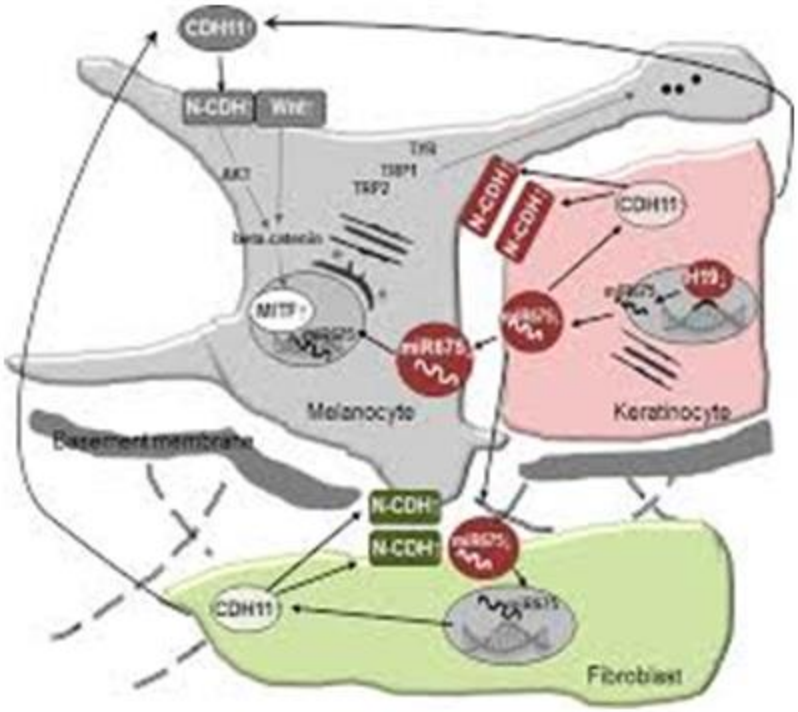


Figure 2: Melanogenesis induced by UV radiation

METHODS

In this discussion, the researcher came across twenty relevant studies published between 2015 and 2019 featuring the latest advances in the treatment of melasma. For purposes of this study, the researcher divided the melasma therapies into three groups – topical, oral, and procedural. There were patients who had to have a combined therapy of either 2 or three of the aforementioned treatments, depending on their respective cases of melasma. The delineation of the types of therapy would make it much clearer to the reader what types of therapy have had a positive outcome and which are relatively new in the management of melasma.

Figure 3: Example of a popular topical treatment for melasma

DISCUSSION

Diagnosis:

Through dermoscopic examination, pronounced hyperpigmentation may be seen in the pseudo-rete ridges in the skin of the patient (Mishra, et al., 2013). When the pigment is epidermal, the hyperpigmentation is accentuated by using a Wood's lamp (Achar, et al., 2011) which can be seen as dermal or mixed melasma (Grimes, et al., 2005). Moreover, to check for melasma on the cellular level will need the reflectance confocal microscopy (RCM) which is a non-invasive technique that detects pigmentary changes in melasma at a cellular level resolution. An increase in hyperrefractile cobblestoning cells in the epidermis leads to hyperpigmented basal keratinocytes on histology (Kang et al, 2010). Epidermal dendritic cells were reported in some patients which corresponds to activated melanocytes. Furthermore, RCM may reveal plump bright cells corresponding to melanophages in the dermis, along with blood and solar elastosis. The differential diagnosis for melasma includes erythema dyschromium perstans, lichen planus pigmentosus, post-inflammatory hyperpigmentation, poikiloderma of Civatte, macular amyloidoses , phototoxic dermatitis,

phytophotodermatitis, pigmented contact dermatitis, drug-induced pigmentation, ochronosis, hori's nevus, argyria, nevus of ota, , ephelides, , erythromelanosis follicularis faciei, discoid lupus erythematosus, and lentigines (Bagherani, et al., 2015).

Pathogenesis:

Melasma's etiology is multifactorial. Laboratory and clinical studies have shown that exposure to UV light can exacerbate and trigger the condition (Achar, et al., 2011). UV light induces the reactive oxygen species (ROS) through the activation of the inducible nitric oxide leading to melanogenesis (Jo, et al., 2009). Moreover, if compared to healthy people, patients with melasma have also been found to have higher markers of oxidative stress (Seckin, et al., 2014). Furthermore, pigmentation has been found to be induced by the presence of visible light. This particular study revealed that sustained pigmentation from visible light can lead to darker skin in a period of over 2 weeks, similar to what pigmentation from UVA-1 light can do over a similar time period (Mahmoud, et al., 2010). A similar study presented the result of flashing visible light at a wavelength of 415 nm for a period of three months - increased pigmentation (Duteil, et al., 2014).

Keratinocytes and fibroblasts stimulate the process of melanogenesis after visible light and UV exposure. The secretion of stem cell factor (SCF), the ligand for the tyrosine kinase receptor, c-kit, happens during light and UV-induced pigmentation which consequently leads to the proliferation of melanocytes as a resulting effect.

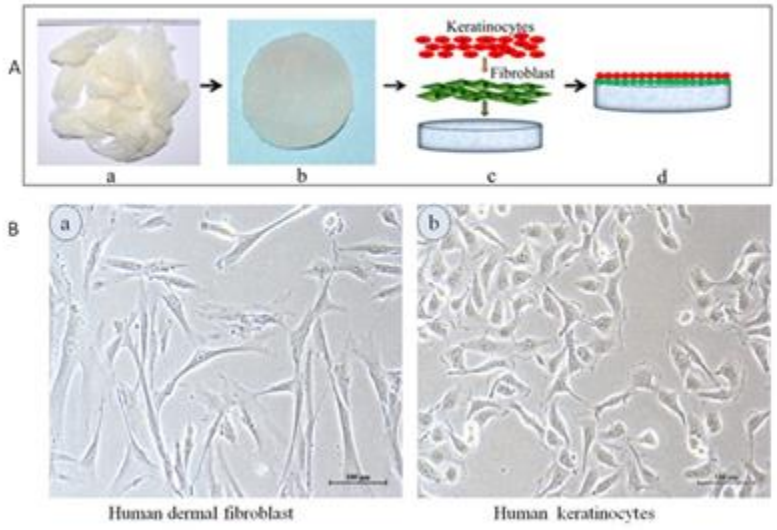
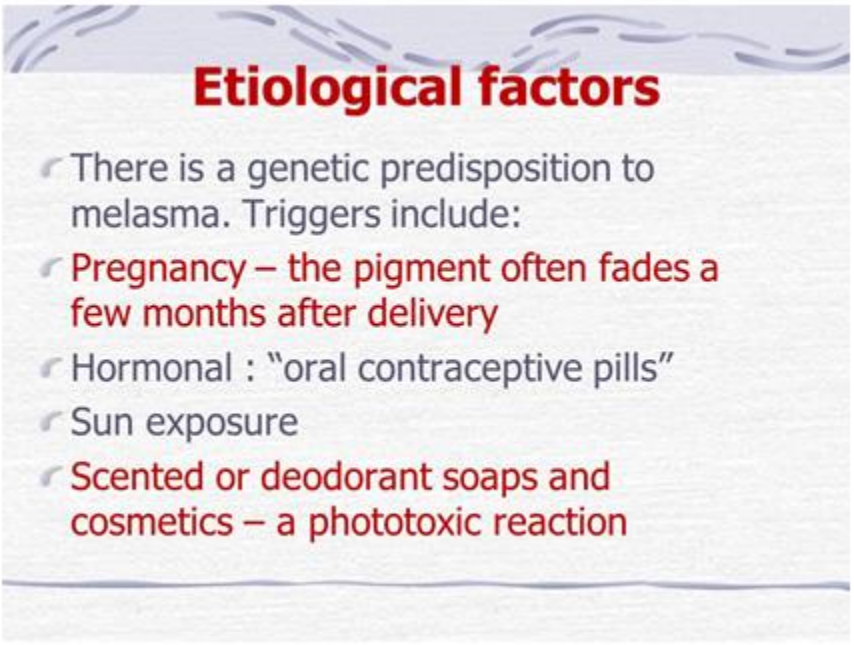


Figure 4: Keratinocytes and fibrolasts

Moreover, his study discussed the effect of increased SCF in the dermis and c-kit in the epidermis in areas of melasma (Kang, et al., 2006) which is exacerbated by increased mRNA levels of melanogenesis-associated genes (Kang, et al., 2011). Increased levels of Wnt signaling-related genes has also been found to be instrumental in melanogenesis especially that Wnt has been linked to the proliferation of melanocyte stem cells – as discovered in further studies (Kim, et al., 2013). Furthermore, human melanocytes in tissue culture have been assisted by the vascular endothelial growth factor (VEGF), a product of keratinocytes after UV

damage (Kim, et al., 2005). This is one of the reasons why there is increased activity of melanocytes in melasma (Lee, et al., 2010). The pathogenesis of melasma also is caused by the downregulation of lipid metabolism-associated genes in lesional skin leading to impaired barrier function as indicated by the results of recent gene and protein expression studies (Kang, et al., 2011).



Genetic predisposition to developing melasma is one of the hypothesis being forwarded putting family history as a vital risk factor. This is bolstered by the findings of these studies which have reported that 55–64% of patients with this condition have a positive family history (Handel., et al., 2014). Genes have also been suggested as responsible for melasma, especially those genes that involve pigmentary, inflammatory, hormonal, and possibly vascular responses. However, this hypothesis has not been proved yet as no genome-wide study has been performed to examine associated genes. However, recent results point to the fact that patients with Fitzpatrick skin type (FST) II and III are less likely to have a positive family history than patients with darker skin types (IV–VI). Another significant player in the pathogenesis of melasma as observed from the increased prevalence with pregnancy, oral contraceptive use and other hormonal therapies is hormonal influences play a significant role in ((Ortonne, et al., 2009). The peri-menopausal state has also been linked to extra-facial melasma (Hexsel, et al., 2014). Significantly increased amounts of the progesterone receptor in the epidermis of affected skin is also another cause as suggested by this immunohistochemical study of the epidermis and dermis of affected and unaffected neighboring skin (Jang, et al., 2010). Another observation made in that study, although its significance to melasma is still unknow is the increased estrogen receptor protein expression in the dermis and around the blood vessels (Tamega Ade, et al., 2015).

In this case–control study, melasma was lined to an increased number of lentigines and nevi (Adalatkah, et al., 2008). Melasma has also been associated with endocrinological diseases like thyroid

disorders. However, the observed prevalence of thyroid diseases, as shown by these studies, have not increased when compared to the general population (Lutfi, et al., 1985).

Histology:

Based on history, melasma has been identified as having three histologic variants: dermal, epidermal, and mixed (Sanchez, et al., 1981). There is a heightened pigmentation all over the layers of the epidermis, mainly in the suprabasilar and basilar layers of the epidermal type.

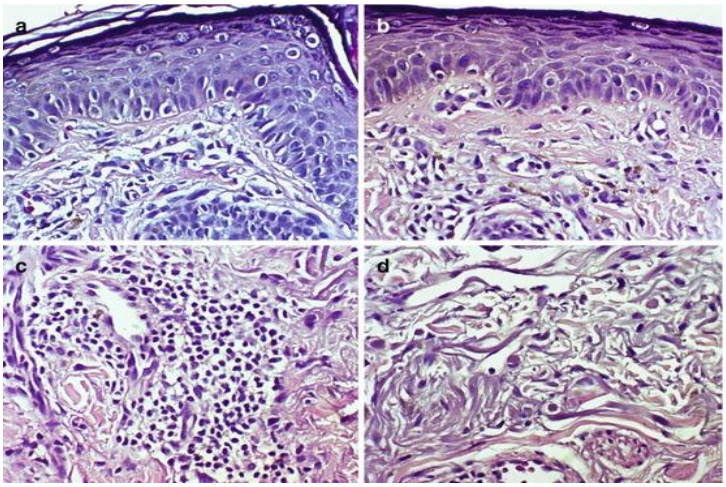


Figure 5: A Histopathology of Melasma in Brown Skin

Usually found in the epidermis, the melanocytes have prominent dendrites, and increased melanosomes, and are generally enlarged (Grimes, et al., 2005).

An increase in melanocyte number occurred in one study. However, most studies report no change in the number of epidermal melanocytes (Kang, et al., 2002). The dermal and epidermal subtypes is categorized using a Wood's lamp which helps highlight the epidermal pigmentation. In the deep and superficial dermis, the dermal subtype has melanophages. Furthermore, in the dermis, a lymphohistiocytic infiltrate may be seen in areas with increased melanin deposition. Solar elastosis and an increase in blood vessels are some of the dermal findings (Bagherani, et al., 2015). Combined histologic features are often displayed by mixed melasma of the dermal and epidermal subtype.

New Advances in Treatment:

This paper is going to discuss the recent advances in the different treatments for melasma including topical, oral, procedural, and combination treatments. These are aimed at various aspects of the pathogenesis of melasma including photodamage, inflammation, vascularity, and pigmentation

New oral and topical treatments

New topical agents:

For the purposes of this discussion, four new topical agents are going to be discussed in this paper. The first one is the ***pigment-correcting serum***. It contains plankton extracts, tetrapeptides, undecylenol phenylalanine, henylethyl resorcinol and niacinamide. It was reformulated to address the

following pathways involved in the induction of hyperpigmentation - melanosome development, melanosome transfer, keratinocyte differentiation and desquamation, melanin synthesis, and melanocyte activation. Its efficacy was found to be comparable to hydroquinone in patients with melasma and post inflammatory hyperpigmentation as found in a randomized, double-blind comparison trial of 43 patients where pigment-correcting serum was compared with hydroquinone 4% (Makino, et al., 2016). The second one is ***flutamide*** which is a nonsteroidal antiandrogen that blocks the action of endogenous and exogenous testosterone by binding to the androgen receptor. This recent experimental study evaluated the efficacy of topical flutamide in patients with melasma. Seventy-four women were enrolled in a parallel, randomized, 16-week trial that compared once daily flutamide 1% with hydroquinone 4%. The use of flutamide led to the improvement of skin hyperpigmentation along with similar efficacy to hydroquinone 4% as revealed in the results of the Melasma Area Severity Index (MASI) and colorimetry scores. Interestingly, the patients given flutamide were more satisfied with the results compared with the group given hydroquinone 4% (Adalatkhah & Sadeghi-Bazargani, 2015). The third one is ***cysteamine*** or cysteamine hydrochloride (ß–mercaptoethylanine hydrochloride) which the body produces naturally and is a degradation product of the amino acid L-cysteine. It is also a radio protector that protects cells from the mutagenic and other lethal effects of ionizing radiation via its direct scavenging effects on hydroxy radicals (Besouw, et al., 2013). Several studies have documented the efficacy of cysteamine in patients with melasma. This randomized, double-blind trial of 40 patients, a significant improvement in melasma lesions was observed compared with patients who were treated with placebo. It assessed the efficacy of 5% cysteamine in 50 patients with melasma and the results showed that cysteamine induced significant reductions in MASI scores at 16 weeks compared with placebo (Mansouri, et al., 2015). The fourth one is ***methimazole*** which causes depigmentation if applied topically. It is more well known as an oral anti-thyroid medication used to treat patients with hyperthyroidism. Methimazole causes skin lightening and because of that, it has been used in patients with melasma and post inflammatory hyperpigmentation. It blocks melanin synthesis and is a potent peroxidase inhibitor. Absorption studies of topically applied methimazole 5% revealed minimal detectable serum levels and no abnormalities (Kasraee, et al., 2008). In another study, methimazole 5% was given daily to 20 patients suffering from epidermal melasma and it did not induce any significant changes in free triiodothyronine levels, free thyroxine and serum thyroid-stimulating hormone. Furthermore, methimazole must not be used as a general cosmetic lightening agent and should only be applied to areas affected by melasma (Kasraee, et al., 2008).

CONCLUSIONS

Despite inroads being made in its modes of treatment, melasma has remained a chronic, therapeutically challenging, and universally relapsing condition. A multimodality approach to treatment is usually used for this disease due to its psychologically devastating effects. The multimodal approach allows the use of exfoliants, photoprotective agents, skin lighteners, resurfacing procedures in severe cases, and antioxidant treatments. This paper has just discussed a plethora of new and varied oral, topical and

combination therapies for melasma and all these warrant additional trials to substantiate their efficacy and safety.

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