Chapter

Melasma: A Review about Pathophysiology and Treatment

Marisa Gonzaga da Cunha and Ana Paula da Silva Urzedo

Abstract

Melasma is a very common disease that is manifested by increased skin pigmentation mostly in the face but also in the décolleté, neck, and arms. It is presented as irregular, light to dark brown spots, placed on the forehead. Cheek bones, mandible, and supralabial region. It usually affects women in higher phototypes (III–V), more commonly at a rate of nine women: one man. Melasma is a multifactorial disease, and we know that some conditions, such as pregnancy, contraceptives, thyroid diseases, hormone replacement, and solar exposure, could be a trigger to develop this illness. Despite not being a serious condition, melasma causes discomfort for those who have it, and it could compromise the patient's quality of life. The goal of this chapter is to understand the pathogenic mechanism of melasma as well as revise the treatments of this disorder.

Keywords: melasma, melasma treatments, melasma oral treatments, laser, pulsed light intense, peelings and melasma, hormones and melasma

1. Introduction

Melasma is a condition that affects millions of individuals around the world, most often women than men, in the proportion of 9:1. Although it is not a serious disease, it has a very important psychological impact on people who suffer from this condition.

It is known to affect people with higher phototypes; it is related to exposure to UV radiation and visible light, as well as thyroid disorders, and the use of contraceptives, hormone replacement, and drugs for epilepsy [1, 2].

2. Methodology

The authors made research on the platform PubMed with the terms: "melasma," "melasma and treatment," melasma and pathophysiology," "melasma and new treatments," "melasma and oral treatments," and "melasma and laser."

More than 10,660 papers were found. The papers included in this chapter have been published in the last 5 years.

3. Objective

The objective of this chapter is to review the pathophysiology of Melasma and discuss both current treatments and the ones about to come.

4. Etiopathogenesis

For a better understanding of pigmentation disorders, it is important to understand the biology of melanocytes, which are neural crest-derived cells. During embryogenesis, melanocytes' precursor's cells, called melanoblasts, migrate along the dorsolateral pathway to reach the epidermis and hair follicles.

Causes for the increase in the production of melanin:

1. Expression of proopiomelanocortin (POMC) and its derivatives by cells within the skin;

2. Number of melanocortin-1 receptors (MC1-R) on melanocytes;

3. Release of diacylglycerol (DAG) from the plasma membrane that activates protein kinase C;

4. Induction of SOS reaction for UVR-induced cell damage;

5. Production of nitric oxide (NO) that activates the cGMP pathway;

6. Production of cytokines and growth factors by keratinocytes [3].

Five main etiopathogenic mechanisms have been detected in melasma:

1. Inappropriate activation of melanocytes;

2. Aggregation of melanin and melanosomes in the dermis and epidermis;

3. Increased number of mast cells and solar elastosis;

4. Basement membrane changes;

5. Increased vascularization.

4.1 Inappropriate activation of melanocytes

The melanocytes are more active in the area of the melasma, and when exposed to UV radiation or visible light, they increase the production of melanin through organelles called melanosomes.

Melanin synthesis is closely related to the enzyme tyrosinase, which, in addition to several other enzymatic processes, will convert tyrosine into eumelanin. After this conversion, melanin will be distributed to the keratinocytes. Keratinocytes, fibroblasts, and other cells of the immune system will secrete paracrine factors related to either inflammatory stimuli or sunlight.

Extracellular matrix (ECM) glycoproteins in peripheral cutaneous nerves can also be affected by melanogenesis. These mechanisms increase the amount of melanin in keratinocytes in the epidermis and macrophages in the dermis.

The receptor for tyrosine kinase (c-KIT) is able to place phosphate groups on the tyrosine residues of other proteins, as well as activate autophosphorylation. The KIT binding membrane (m-KIT) and its soluble form (s-KIT) have demonstrated antagonistic mechanisms *in vivo* and *in vitro*. The binding of stem cell factors (SCF) to m-KIT induces melanogenesis, while the s-KIT production suppresses melanogenesis in human melanocyte culture.

UVB radiation increases SCF and m-KIT levels and decreases s-KIT expression levels, resulting in increased melanogenesis. The increase in SCF levels in the dermis together with the increase in c-KIT in the epidermis of patients with melasma is partially mediated through cell-cell interactions between melanocytes and fibroblasts.

Fibroblasts secrete Wnt signaling modulators, which stimulate both melanogenesis and melanosome transfer. The Wnt/β-catenin pathway includes a large family of proteins with different cellular functions, such as melanoblast migration, proliferation, and pigmentation induction. Wnt1 is a beaded transmembrane receptor binding, which promotes the accumulation and stabilization of β-catenin. When incubated in cell culture, melasma fibroblasts also enhance melanogenesis, with overexpression of nerve-derived growth factor.

Another implicated factor is the UV radiation that induces cyclooxygenase (COX-2). COX-2 knock-down in melanocytes results in decreased expression of tyrosinase, protein-1 (TRP-1), TRP-2, glycoprotein 100, and MITF. Besides, COX-2 siRNA-transfected melanocytes show a reduction of alpha MSH.

Despite the whole face being exposed to the sun, it can be observed that only some areas, mainly the ones rich in sebaceous glands, will be affected by melasma. This may be due to the fact that these appendages have the ability to synthesize vitamin D and secrete various cytokines and growth factors. Sebocytes are controlled by alpha-MSH, which suggests a connection between these cells and melanocytes. Moreover, skin surface lipids undergo oxidation by UVR, which can activate melanin synthesis in melanocyte culture.

There is also a marked increase in superoxide dismutase activity, as well as a significant reduction in glutathione levels in melasma patients, leading to the belief that these people suffer from increased oxidative stress [4, 5].

4.2 Aggregation of melanin and melanosomes in the dermis and epidermis

Biopsies of areas affected by melasma demonstrate melanin increase in both epidermis and dermis when compared to perilesional skin.

Rupture of the basement membrane causes melanocytes to descend into the dermis as free melanocytes (melanocyte effusion). On electron microscopy, it can be seen that melanocytes in the area with melasma have more dendrites than those in normal skin. They also have more mitochondria, golgi complex, rough endoplasmic reticulum, and ribosomes in their cytoplasm [4].

4.3 Increased number of mast cells and solar elastosis

Solar elastosis is the abnormal accumulation of elastic tissue in a dermis that is chronically exposed to the sun, and this occurs in 83–93% of patients with melasma.

Mast cells are most prominent in the elastotic areas of the skin affected by melasma. In the development of solar elastosis, mast cells have been shown to induce fibroblasts to produce elastin, either directly or indirectly through other cells or cytokines. Mast cells are capable of inducing vascular proliferation by various angiogenic factors, such as VEGF, basic fibroblast growth factor (bFGF-2), and transforming growth factor beta (TGF-β).

Mast cell tryptase and granzyme B are involved in basement membrane degradation after UV irradiation. Mast cells are involved with solar elastosis, vasodilation, and basement membrane rupture, which can be seen in histology [4].

4.4 Basement membrane changes

The rupture of the basement membrane (BM) is described in several studies. Vacuolar degeneration of basement cells and vacuolar degeneration of the basement membrane and subbasement membrane region have been described.

Chronic exposure to UV radiation results in increased levels of matrix metalloproteinase 2 (MMP2), which degrades collagens IV and VI, leading to basement membrane rupture. This allows melanocytes to descend through the dermis, which is known as pendant melanocytes, and they can contribute to pigmentation both during their migration into the dermis and after trauma or treatment.

BM damage, due to aging, environment, and iatrogenic factors, could facilitate the migration of active melanocytes and melanin to the dermis, leading to the accumulation of free melanin or melanophages, thus explaining the persistent hyperpigmentation in melasma.

BM degradation is also mediated by mast cells as seen above. The degradation of these cells releases tryptase that can activate MMPs and cause direct damage to extracellular matrix proteins.

Granzyme B, a serine protease expressed by a variety of immune and nonimmune cells (including mast cells), accumulates in the extracellular space during chronic inflammation and cleavage of various extracellular matrix proteins, possibly leading to the ECM degradation after UV irradiation.

Melasma presents an accumulation of photodamaged fibroblasts, which leads us to believe that the aging caused by UV radiation may be involved in the genesis of this disease.

BM degradation may facilitate the transfer of multiple growth factors between dermis and epidermis, which could lead to persistent hyperpigmentation [4].

4.5 Increased vascularization

A pronounced increase in vascularity is seen in melasma, and this can also be observed in various inflammatory conditions, including the response to UV radiation.

Vascular endothelial growth factor (VEGF) is increased in the vessels in areas affected by melasma. Normal human melanocytes express VEGF receptors in vitro. Some of these receptors are functional, suggesting that VEGF plays a role in melanocyte behavior in the skin.

VEGF binds to specific receptors, which are also found on endothelial cells that have been shown to stimulate pigmentation through the production of endothelin 1. Endothelin 1 is released by the endothelium of microvessels inducing melanogenesis, characterized by MIFT phosphorylation and increased tyrosinase levels. VEGF also influences melanocytes by stimulating the release of arachidonic acid and the

subsequent activation of phospholipase A. The increased production of melanin may result from metabolites that are secreted in the arachidonic acid pathway. VEGF may also partially affect pigmentation through positive regulation of the expression of protease-activated receptors (PAR-2), especially in melasma patients with prominent telangiectatic erythema.

Sex hormones alone, mainly estrogen, are not capable of inducing melasma pigmentation, but they act synergistically with UVB radiation. However, estrogen can perpetuate hyperpigmentation by increasing vascularity, which, in turn, stimulates endothelin 1 secretion. As the sensitivity of cells to sex hormones is an individual factor, this could probably explain the variability in susceptibility to developing the disease [2, 4].

4.6 The role of visible light in melasma

A follow-up study by Regazzetti *et al.* was performed on normal human melanocytes (NHMs) in order to understand the mechanisms of blue-light-induced hyperpigmentation. Blue light has been shown to stimulate melanogenesis by acting on the microphthalmia-associated transcription factor (MITF), the master pigmentation gene.

Photons are absorbed and converted into a cellular response through a class of G-protein-coupled receptors called opsins, which are light-activated. Traditionally, opsins are well known for their role in the photoreception of the eye. However, recent studies have shown that rhodopsin (OPN2), cone opsins (OPN1-SW), encephalopsin/opsin-3 (OPN3), and neuropsin (OPN5) are expressed both in melanocytes and keratinocytes. Notably, OPN2 and OPN3 were significantly more abundant than other opsins. In Regazzetti's study, after irradiating normal human melanocytes with blue light, OPN3 was the only significantly expressed opsin. To investigate whether OPN3 could mediate the effects of blue light melanogenesis, OPN3 was knocked down using small interfering RNA (siRNA). In NHMs with siRNA directed against OPN3, blue light irradiation no longer had an effect on MITF phosphorylation [6].

5. Treatment

As melasma has a lot of pathways to induce melanogenesis, the treatment must include many topical and systemic drugs. Antioxidants and photo protectors, as well as lightning, laser, peeling, and other procedures are usually indicated.

In the paragraph below, we will discuss the indicated treatments and their mechanisms of action (**Tables 1** and **2**).

Treating melasma is a challenge, and it is known that the treatment must address the various mechanisms of hyperpigmentation of this condition.

The most frequently cited depigmenting topical agent in literature is still hydroquinone. It works by inhibiting the conversion of 1–3,4-dihydroxyphenylalanine into melanin by competitive inhibition of tyrosinase. Although the risk seems to be only theoretical, there might be side effects, such as exogenous ochronosis, permanent depigmentation, and potential carcinogenic risk.

Up to now, other depigmenting agents considered safer to date are 4-n-butylresorcinol, niacinamide, ascorbic acid, resveratrol, azelaic acid, and kojic acid. However, depigmenting agents alone are not able to improve the photoaging issue closely related to melasma. Therefore, antiaging agents should be associated in order to try

Active	Mechanism of action	Drug concentration
Hydroquinone	Tyrosinase inhibitor	2–4%
4-N-butyl resorcinol	Tyrosinase inhibitor	2–4%
Niacinamide	Reduction of melanosome transfer anti-inflammatory antiaging	5–10%
Ascorbic acid	Antioxidant Tyrosinase inhibitor photoprotective effects	5–25%
Azelaic acid	Antiaging effect antiaging	10–20%
Kojic acid	Tyrosinase inhibitor trapping free radicals	1–4%
Triple combination Hydroquinone tretinoin, fluocinolone acetonide	Depigment effect Tyrosinase inhibitor Anti-inflammatory effect	4%, 0,05% 0,01%
Arbutin	Tyrosinase inhibitor	1–3%
N-acetyl-4 s cysteamine phenol (NCAP4%)	Antioxidant effects	5%
Resveratrol	Melanogenesis inhibitor Tyrosinase inhibitor	1%

Table 1.
Mainly topical treatments for melasma.

Korean red ginseng powder	Korean red ginseng powder shows good tolerability and beneficial effects for melasma
Polypodium leucotomos	Oral PLE is not significantly better than placebo as an adjunct to topical sunscreen for melasma oral polypodium leucotomos extract appears to be a safe and effective adjunctive treatment in combination with topical hydroquinone and sunscreen for melasma
Pycnogenol/grape seed extract	Pycnogenol 75 mg is therapeutically effective and safe in patients suffering from melasma Grape seed extract is safe and useful for improving chloasma
Vitamin E	Vitamin C + E combination treatment has significantly better results than vitamin C alone for chloasma Oral procyanidin + vitamins A, C, and E are safe and effective for epidermal melasma.
Refs. [7–10].	

Table 2.
Oral treatments for melasma.

and correct the photodamage, as this may be related to the frequent recurrences of this condition.

The triple combination containing hydroquinone (HQ) 4%, 0.05% tretinoin, and 0.01% fluocinolone acetonide is the only FDA-approved drug that contains HQ for the treatment of melasma. Tretinoin has depigmenting and antiaging effects. Steroids inhibit the secretion of both ET-1 and granulocyte-macrophage colony-stimulating factor (GM-CSF), acting against the inflammation present in melasma, which is related to photodamage and melanogenesis. Azelaic acid is an anti-inflammatory agent with depigmenting properties that have been reported to reverse the aging of human fibroblasts after PUVA induction. It also inhibits the secretion of MMP-1 and growth factors, such as the hepatocyte growth factor (HGF) and the

SCF, through the activation of the peroxisome proliferator-activated gamma receptor (PPARy).

Wnt antagonists, including cardamonin and FTY720 (fingolimod), have been shown to suppress melanogenesis in vitro. A recent study has demonstrated that andropholide inhibits tyrosinase activity and melanin production via the Beta-catenin degradation into B16F10 in the UVB-induced melanoma cells in guinea pigs [6].

5.1 New topical agents that target hyperactive melanocytes

Linoleic acid: has selectivity for tyrosinase in hyperactive melanocytes and decreases UVB-induced hyperpigmentation.

Ascorbic acid: decreases dopaquinone oxidation into DHICA dihydrxyindole-2-carboxylic acid), lowers tyrosinase activity, reduces dermal damage, promotes collagen synthesis, and has both antioxidant and photoprotective effects, thus reducing pigmentation.

N-acetyl-4S cysteamine phenol (NCAP4%): less irritating and more stable than hydroquinone, is a tyrosinase inhibitor in hyperactive melanocytes, interfering with the thiol system, decreasing intracellular glutathione, and favoring pheomelanin synthesis [11].

5.2 New agents targeting melanogenesis

Aloesin: aloe vera extract that inhibits the conversion of tyrosinase into DOPA and of DOPA to dopachrome.

Rucinol (4-n-butylresorcinol): a phenolic derivative that inhibits tyrosinase and TYRP-1.

Flavonoids: benzopyrene derivatives, which are competitive inhibitors of tyrosinase with anti-inflammatory effects and antioxidant properties. Hesperidin: a flavonoid that protects against free radical-induced damage caused by UVR.

Epigallocatechin gallate: a phenolic compound, extracted from green tea, which inhibits melanogenesis and has a significant anti-inflammatory, antioxidant and anti-cancer effect.

Ellagic acid: a polyphenol derived from green tea, strawberries, and pomegranate that can inhibit tyrosinase and melanocytic proliferation.

Gentisic acid: a compound extracted from the gentile roots that inhibit melanin synthesis.

Hydroxycoumarin: occurs naturally in lactones that inhibit tyrosinase due to their antioxidant action. Umbelliferone (7-hydroxycoumarin) has anti-inflammatory action.

Cinnamic acid: derived from ginseng, inhibits tyrosinase and is more potent than hydroquinone.

Antisense oligonucleotides: act as a bleaching agent by downregulating the production of enzymes that involve melanogenesis and decrease the activity of DOPA oxidase [11].

5.3 Agents against reactive oxygen species (ROS) and inflammation

Liquorice extract: derived from the root of *Glycyrrhiza glabra*, inhibits melanin synthesis and disperses melanin, in addition to decreasing ROS production. It has anti-inflammatory effects and decreases UVB-induced hyperpigmentation in guinea pigs after 3 weeks of use.

Acidified amino acid peels: peels with a pH close to the skin's pH have antioxidant and tyrosinase inhibitory effects.

Orchid extract: strong antioxidant activity. It has proven to be as effective as vitamin C in a study with 48 melasma patients.

Coffeeberry extract: has antioxidant properties and reduces hyperpigmentation as well as photodamage.

Mulberry extract: derived from the *Morus alba*, its extract is a free radical chelator and a tyrosinase inhibitor.

Pycnogenol (oral): derived from the bark of *Pinus pinaster*, it presents antioxidant and anti-inflammatory activity.

Polypodium leucotomos (oral): this extract works by inhibiting UVR-induced ROS, including superoxide anions.

Alpha tocopherol: strong anti-inflammatory and marked antioxidant activity.

Proanthocyanidin (oral): grape seed extract with antioxidant action. A study conducted on women submitted to a 6-month treatment has shown whitening in 10 out of 12 women [11].

5.4 Melanosomal transfer: Protease-activated receptor2

Niacinamide or vitamin B3: active amide of niacin, interferes with melanosome transfer to the surrounding keratinocytes by inhibiting PAR-2.

Liquiritin: leads to a skin-lightening effect through dispersion of melanin.

Soymilk, soybean (topical): the serine protease inhibitors, such as soy trypsin inhibitor (STI) and Bowman-Birk inhibitor (BBI), found in soybeans have been shown to inhibit melanosome phagocytosis by keratinocytes via the inhibition of PAR-2. Newer agents that target the defective barrier, such as soy topically applied and active soy moisturizers containing nondenatured serine protease inhibitors (STI and BBI), can decrease UVB-induced pigmentation by restoring the skin barrier [11].

5.5 Agents targeting the vascular component

The systemic tranexamic acid (TXA) is an anti-fibrinolytic agent, which has been shown to be an inhibitor of both UV-radiation-induced melanogenesis and neovascularization, by blocking the plasminogen activator and plasmin activity. Oral administration is at a dose of 250 mg from 2 to 3 times a day for 2 to 3 months, with a significant decrease in both melanin and erythema indexes in the skin with melanin lesions. Histology demonstrates a decrease in pigment, number of vessels, and mast cells. There is a decrease in ET-1 expression. Despite being well tolerated, we must be aware that this drug has, in theory, thrombogenic potential. TXA can also be injected in intradermotherapy associated with lasers and microneedling, but there are not enough studies and the results are still limited [11].

5.6 Agents that target mast cells

5.6.1 Tranexamic acid

Zinc: reduces mast cell secretion and has an antioxidant effect [11].

5.7 Agents with hormonal targets

Flutamide is an antiandrogenic agent that can influence alpha-melanocyte-stimulating hormone and cyclic adenosine monophosphate, which are key regulators of melanogenesis [11].

5.8 Newer agents with unique mechanisms: Potential targets of the future

Curcumin (topical) is a bioactive compound extracted from the rhizome of *Curcuma longa* and its use is well-established in traditional Chinese medicine for the treatment of various skin diseases. It inhibits UVB-induced production of ROS and the expression of matrix metalloproteinase in vitro by blocking the activation of the UVB-induced mitogen-activated protein kinase, the nuclear factor-κB, and the AP-1 transcription factor signal pathway. Curcumin gel has been useful in the repair of photodamaged skin as well as for the associated pigmentary changes and solar elastosis. In view of its anti-inflammatory, free radical scavenging, and UV-protective activities, curcumin may serve as a new skin-lightening agent in the future, both in topical and oral preparations.

Lignin peroxidase (LP, topical use) is an enzyme derived from the fungus Phanerochaete chrysosporium. Since lignin is structurally similar to melanin, lignin-degrading enzymes can be utilized to decolorize melanin. Lignin peroxidase is marketed as a formulation containing the active enzymatic component and its activator (hydrogen peroxide), causing the destruction of eumelanin.

Treatments with technologies, such as intense pulsed light (IPL), fractional laser, 1550 nm nonablative laser, Q-Switched neodynium-doped yttrium aluminum garnet laser (QSNYL), pulsed dye laser (PDL), and copper-bromide laser, have shown positive results. Laser toning using collimated, low fluence, 1064 nm QSNYL removes melanosomes and damages the dendrites of melanocytes without destroying the entire melanocyte ("subcellular selective photothermolysis"). Nevertheless, the accumulation of energy from several sessions can cause depigmented mottling lesions similar to scars, which makes melanogenesis difficult [11, 12].

Newer sunscreens: visible light (VL) and infrared light (IR) have been shown to play an important role in hyperpigmentation, especially in the darker skin types (III, IV, or V). VL may induce the production of ROS, leading to DNA damage. IR light provokes the activation of the endothelin receptor B and the mitogen-activated protein kinase, which facilitates melanogenesis. Sunscreens containing iron-oxide are effective against hyperpigmentation induced by VL.

Other new UV-VL sunscreens that allow absorption of the radiation in the VL spectrum and systemic antioxidants, such as vitamin A, C, and E, carotenoids, and beta-carotene, may provide additive protection. Nonorganic and organic filters that absorb or reflect IR are currently available. Also, topical antioxidants may be able to offer some protection against IR-related damage. However, their clinical efficacy remains to be determined.

6. Discussion

Melasma is a multifactorial disease and until now there is not a universal treatment to solve it. At the moment, the first choice to treat melasma is the triple association

of tretinoin, hydroquinone, and fluocinolone acetonide associated with a broad-spectrum pigmented sunscreen, but this treatment presents some side effects, such as exogenous ochronosis and depigmentation, in confetti when used for a long time. Despite all the knowledge about the pathophysiology of melasma, we do not have the cure for the disease. There are many new drugs with different targets to control the pigmentation, but, unfortunately, there is often resurgence of melasma. The discovery of the influence of the vessels in the pathogenesis of melasma was very important, and there are some papers about the use of oral tranexamic acid with encouraging results, but these treatment regimens must be reserved for refractory cases.

Concerning peeling, laser, and other technologies, some publications show good results, but there is not a big study with a long follow-up period to confirm efficacy. It is very important to bear in mind that melasma is a chronic disease and these treatments, which are very expensive for the patients, could sometimes generate false expectations.

7. Conclusion

Melasma is a very common disease that is a challenge to manage. More research about de pathogenesis of the disease is necessary, leading to the development of new drugs and therapies to control it.

To sum up, the most interesting approach to treat the disease involves a rotation of treatments and removing the causes that worsen the condition, as well as teaching the patient to make up and camouflage the lesions.

8. Key points in this chapter

1. Melasma is a multifactorial disease.

2. Sunscreen with pigment has a very important role in the treatment.

3. Topical treatment with different targets in the pathophysiology of melasma could control the disease.

4. Laser, peelings, and micro-needling could be an interesting adjuvant treatment.

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