

Hyperpigmentation and Melasma: A Physiopathologic Review for the Clinical Dermatologist

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Melasma is a common acquired skin disorder that is characterized by localized hyperpigmented patches in sun-exposed skin. Histologically, affected areas show an increased production and transfer of melanosomes to keratinocytes, augmented arborization of melanocytic dendrites, and enlarged melanocytes that are increased in number. Although melasma has many well-recognized etiologic factors (eg, UV light exposure and sex hormones), its exact pathogenesis is unknown. Published reports on the specific aspects of pigment formation and regulation in melasma lesions are sparse. This article reviews the physiology of a healthy pigmentary system and highlights published data on the possible pathways involved in the abnormal pigmentation found in melasma.

Components of human skin color include melanin, blood in superficial capillary vessels, collagen, and other internally and externally produced chemicals, such as bilirubins and carotenoids.¹ Variations of any of these components could result in marked changes in skin color. Hyperpigmentary disorders are very prevalent and a frequent reason for dermatologic visits. Melasma is one of the most common of these conditions and occurs mainly in individuals of Hispanic and Asian descent. Although major etiologic factors in the pathogenesis of melasma have been described, the exact causes of this localized hyperpigmentation are not yet fully understood. Melasma is a benign skin condition that may severely

affect a patient's quality of life.² Efforts to better understand this condition may help increase its treatment options as well as decrease its relapse rate.

The Human Pigmentary System

Melanin is a complex polymer produced by melanocytes.¹ After melanin is produced, melanocytes pack the pigment into melanosomes and pass them into surrounding keratinocytes.³ Melanocytes are located in the basal layer of the epidermis, and their related keratinocytes form the cutaneous pigmentary system. The cutaneous pigmentary system provides protection from UV radiation. Additionally, the cells that comprise this system participate in many superficial inflammatory reactions.⁴

Melanin absorbs UV radiation across a wide spectrum but is particularly effective in absorbing wavelengths from 280 to 320 nm. This absorption spectrum is similar to that of main nucleic acids and proteins,⁵ which suggests that melanin plays an important role in protecting nuclear DNA from sun damage.

Melanocytes are genetically programmed to produce certain types and amounts of melanin, which yield a person's baseline skin color. Two types of melanin have been described: *eumelanin*, a brown or black pigment synthesized from tyrosine, and *pheomelanin*, an orange pigment synthesized from tyrosine and cysteine.^{1,6,7} Human skin can present both types of melanin, with a predominance of either one or the other.^{7,8} A person's constitutive skin color is established by the amount of eumelanin and pheomelanin produced by the epidermal melanocytes, the rate of transfer of melanin-containing melanosomes to keratinocytes, and the relative amounts of eumelanin and pheomelanin within the epidermis.^{1,6,9,10} The type of melanin produced is controlled by 2 genes: the melanocortin 1 receptor, a G protein that is coupled with the 7-pass transmembrane receptor expressed on cutaneous melanocytes, and the antagonist ligand agouti.¹¹ The melanocortin 1

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receptor gene is the only identified gene that explains phenotypic variance in human pigmentation.¹¹

Results of a recent study have shown a significant inverse correlation between constitutive skin pigmentation and DNA damage after UV radiation exposure.¹² Constitutive pigmentation is photoprotective and reaches a maximum sun protection factor of 10 to 15 in dark-skinned individuals.⁷ The low melanin content in the keratinocytes of light-skinned people gives them a relative sensitivity to the sun. Another factor that increases UV radiation susceptibility in the light-skinned population is the predominant production of pheomelanin. Pheomelanin is a poor free radical scavenger and can even generate oxygen radicals on exposure to UV radiation, which contributes to additional DNA damage.^{5,7,13}

Sunlight and hormones can increase the amount of melanin in the epidermis, causing the appearance of the so-called facultative skin color.¹ Pathologic occurrences in which abnormal melanocytes increase or become markedly dysfunctional can influence constitutional and/or facultative pigmentation. Melasma, which presents as marked localized pigmentation of the skin, is an example of such a pathologic occurrence and is a common complaint of patients seeking dermatologic care.

Melasma

Melasma is characterized by darkly pigmented patches confined to sun-exposed areas, especially over the bony prominence of the malar region and extension surface of the arms.^{4,14,15} Lesion color may vary from brown to grayish blue, depending on the constitutive skin color, melanin amount, and distribution on the skin. Melasma lesions are determined by an increased production and transfer of melanosomes to keratinocytes, augmented arborization of melanocytic dendrites, and, according to some authors, an increased number of melanocytes.^{4,15}

Results of a recent study by Grimes et al¹⁶ examining the effects of Mel-5 monoclonal antibodies in patients with melasma showed increased epidermal/dermal deposition of pigment in the hyperpigmented areas of all study participants. In contrast, no significant quantitative increases in melanocytes were observed; however, individual melanocytes were enlarged and intensely stained, with prominent dendrites present. Mild perivascular lymphohistiocytic infiltrates were present in about 75% of the hyperpigmented areas.¹⁶

Some melasma lesions, especially those with mandibular distribution, may present associated signs of severe sun damage.¹⁷ Once established, the lesions usually maintain their limit without spreading to the surrounding areas.⁴

Melasma can be classified into 4 types, according to pigment distribution: epidermal, dermal, mixed epidermal/dermal, and indeterminate.¹⁴ Epidermal lesions are recognized by the enhanced color contrast between affected and healthy skin under Wood lamp (UV light) examination; dermal lesions are blue to gray and do not show enhanced color contrast when compared with healthy skin under Wood lamp examination; mixed epidermal/dermal lesions show both patterns; and indeterminate lesions, which are found in Fitzpatrick skin types V and VI, are not discernible from healthy skin under Wood lamp examination. In patients with indeterminate-type melasma, constitutional pigmentation obscures the detection of abnormal melanin deposits.¹⁴

Although melasma is a benign skin condition, it deserves special attention because of its potential negative social and emotional effects. In a sample of 102 women, the 3 quality-of-life parameters most affected by melasma were social life, recreation, and emotional comfort.² It is interesting to note that the negative effects of melasma on patient quality of life may not correspond with the clinical severity assigned by the physician.²

Pathogenesis of Melasma

The exact mechanism by which melanocytes are functionally altered, which gives rise to the hyperpigmented patches found in melasma, is not fully elucidated. However, evidence suggests that internal and environmental factors may be responsible for triggering, maintaining, and relapsing lesions.¹⁸ These factors include genetic influences, UV radiation exposure, pregnancy, oral contraceptives, estrogen/progesterone therapies, thyroid dysfunction, cosmetics, and medications such as phototoxic and antiseizure drugs.^{4,14,16,19} In patients with melasma, sexual hormones and UV radiation act synergistically in genetically predisposed individuals, favoring the development of hyperpigmented areas.

Sex Hormones

Female sex hormones are thought to be the main cause of or influence in the development of melasma. Studies have shown that estrogen increases tyrosinase activity and the number of melanocytes *in vitro*.²⁰ Skin cells present receptors for estrogen and progesterone, with higher expression in the facial areas compared with other regions.^{4,21} This receptor distribution may explain the preferential location of melasma.⁴ Moreover, results of studies examining the effects of female sex hormones in patients with idiopathic melasma show a mild increase in

luteinizing hormones and a slight decrease in serum estradiol compared with controls.⁴ This finding suggests that mild ovarian dysfunction may be associated with increased pigment in genetically predisposed individuals. Results of similar hormonal studies performed in male patients with idiopathic melasma showed a significant increase in luteinizing hormones ($P, .05$) and a decrease in testosterone compared with healthy controls ($P, .02$), suggesting testicular resistance.²²

Melasma usually starts after puberty and peaks when patients are in their late 20s or early 30s; the condition is influenced greatly by pregnancy and the intake of oral contraceptive hormones. Partial remissions may occur, especially after parturition or discontinuation of oral contraceptives. When melasma begins during pregnancy, it usually disappears several months after delivery. The hyperpigmentation may or may not recur in subsequent pregnancies. If pigment persists after delivery and the end of lactation, the patient's lesions will probably recur or worsen if oral or hormonal contraceptives are prescribed.⁴

Physiologic fluctuations of gonadotropin levels also have been implicated in the pathogenesis of melasma. During pregnancy, increased melasma prevalence, darkening of the abdominal midline, and nevi changes seem to be secondary to melanocyte response to circulating estrogens.^{23,24} Accordingly, many cases of melasma regress after menopause and ovariectomy.⁴ However, the exact impact of these physiologic changes on the pigimentary system is not fully understood.

α -Melanocyte-Stimulating Hormone

α -Melanocyte-stimulating hormone (α -MSH) is derived from pro-opiomelanocortin, a protein found in the pituitary gland of mammals. Of the 5 described types of MSH receptors,¹ the melanocortin 1 receptor is present on melanocytes and determines the pigimentary phenotype, which controls the switch from eumelanin to pheomelanin^{8,25}; the other types of receptors can be found in various tissues, such as the hypothalamus gland, gut, adrenal gland, brain, muscle, and adipose tissue.²⁶ Plasma levels of α -MSH respond to seasonal sun exposure and, as described for other hormones and neuropeptides, to stress.²⁷ However, the relevance of this hormone in the physiologic control of human pigmentation remains unclear because the circulating levels of α -MSH in humans are low; thus, it is not possible to explain pigimentary differences between individuals in terms of alterations in the level of circulating α -MSH.⁵

In addition to influencing the pigimentary system, α -MSH affects the inflammatory system and the immune response

by interacting with melanocytes and inflammatory cells.^{1,6,28} It is well established that α -MSH antagonizes interleukin 1, interleukin 6, and tumor necrosis factor α , leading to potent anti-inflammatory effects.⁵

Some experimental data suggest that in addition to estrogen and progesterone, α -MSH could influence the hyperpigmentation present in patients with melasma.²⁵ Im et al²⁹ showed that the α -MSH antigen is highly expressed in keratinocytes within lesions, which suggests that α -MSH plays a key role in the pathogenesis of melasma. Furthermore, the expression of MSH receptors is modulated by α -MSH levels, UV radiation, and reproductive hormones (mainly estrogens).²⁵ Melanocytes stimulated by α -MSH show increased formation and transference of melanosomes.¹ α -MSH also stimulates tyrosinase activity and eumelanin synthesis. Increased blood levels of α -MSH have been found in patients treated with UV radiation, and tanning induced by UV radiation is reduced in individuals with hypopituitarism.¹ The fact that α -MSH is present in the placenta during the second and third trimesters of pregnancy provides additional indirect evidence of its role in the pathogenesis of melasma.³⁰

Environmental Factors

The key environmental factor in the development of melasma is exposure to UV radiation. UVB irradiation of healthy melanocytes inhibits melanocyte proliferation resulting from an arrest in the gap 2 phase of the cell cycle.⁶ However, cells that are affected by melasma have increased tyrosinase activity and melanin content.⁶ Such data support the results of a histopathologic study of melasma lesions by Grimes et al¹⁶ that showed normal amounts of melanocytes in all affected areas, with enlarged melanocytes and an increased number of melanosomes and prominent dendrites.

Melanogenesis induced by UV radiation is thought to occur after direct damage to the DNA of healthy melanocytes and after synthesis (or activation) of the cytokine network related to the proliferation and survival of melanocytes.³¹ MSH and corticotropin, for example, can be synthesized by affected keratinocytes and melanocytes.^{25,31} It is not clear, however, which wavelength is responsible for triggering and maintaining melasma lesions. UVB radiation is a potent stimulator of melanin formation by means of paracrine factors produced by exposed keratinocytes, particularly the basic fibroblast growth factor and endothelin 1.³¹ The role of UVA radiation has less supportive experimental evidence, but UVA-induced pigmentation is probably secondary to diverse

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cellular mechanisms. Cultured human melanocytes that are in contact with UVA-exposed keratinocytes increase DNA synthesis in a dose-dependent manner. This event is probably mediated by granulocyte/macrophage colony-stimulating factor.³¹

Conclusion

There is much to learn about the exact cause of melasma. The contributing factors are many, with individual, sporadic, and constitutional factors interfering in the development of the disease. Despite its benign clinical features, melasma has negative effects on an individual's quality of life. The therapeutic management of melasma has been directed at slowing the proliferation and growth of melanocytes, inhibiting the formation of melanosomes, and promoting their destruction. This approach traditionally involves the triad of sun block, lightening agents, and time.³² Although this method has shown positive results—mainly when applied in a rotational system—many of these therapies are not effective and have unpredictable results and/or undesirable side effects. Understanding the factors responsible for skin discoloration and the subsequent interference of these factors may reveal new treatment perspectives that have long-lasting, effective results.

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