

Comprehensive Evaluation of Pathogenesis, Risk Factors and Current Therapeutic Strategies in Melasma: A Clinical and Molecular Perspective

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ABSTRACT

Melasma, an acquired facial hyperpigmentation of a chronic nature, presents a clinical and dermatologic enigma of considerable relevance. This article focuses on a comprehensive review of the underlying pathogenesis of melasma from a molecular and clinical perspective, exploring its multifactorial etiology and the triggering elements that converge in the cascade of biochemical and cellular events that result in its distinctive clinical manifestation. Known risk factors such as excessive sun exposure, hormonal imbalances and genetic predisposition are thoroughly discussed, unraveling their relative contribution and complex interplay in the development of melasma.

In addition, a critical analysis is made of current therapeutic strategies, ranging from conventional topical approaches to more advanced modalities such as laser therapy and technology-based treatments. The efficacy, safety and limitations of these modalities are examined, considering variations in patient response and the durability of the results obtained.

Ultimately, this article seeks to provide a comprehensive synthesis of contemporary advances in the understanding and management of melasma, with the aspiration of guiding dermatologic health care professionals toward more accurate and individualized approaches in the diagnosis and treatment of this complex skin condition.

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INTRODUCTION

Melasma, an intriguing and clinically challenging dermatologic entity, is positioned as a paradigm of acquired cutaneous hyperpigmentation. Its global prevalence and its impact on the quality of life of affected individuals give significant clinical and scientific significance to this skin condition. Despite the apparent benignity of its non-inflammatory nature, melasma masks a complex amalgam of etiopathogenic factors, characterized by the synergistic interaction of genetic predispositions, hormonal imbalances, environmental influences and photoinduced reactions.¹

In this context, the present article pursues the meticulous and comprehensive exposition of the scientific and clinical underpinnings underlying melasma. Through an in-depth exploration of the molecular, cellular and physiological aspects, it seeks to unravel the intricate mechanisms that orchestrate the appearance and evolution of this

hyperpigmented condition. A detailed understanding of the processes involved not only elucidates the underlying pathogenesis, but also lays the foundation for more insightful and personalized diagnostic and therapeutic strategies.¹

Consequently, this holistic inquiry into melasma becomes an essential precept for medical professionals and scientists dedicated to the dermatological field. Expanding knowledge regarding the melanic interplay between genetic, hormonal and environmental factors not only enriches the understanding of this clinical entity, but also potentially unlocks innovative therapeutic approaches that address the underlying causes rather than just the apparent symptoms. Ultimately, this review aims to catalyze a reformulation of conventional approaches to melasma, in the interest of improving the quality of care provided to patients and encouraging continued research in this intriguing dermatologic field.^{1,2}

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MOLECULAR ASPECTS

Melasma, a dermatologic entity of considerable complexity, reveals its intricate enigma through an analysis at the molecular level, revealing a melting pot of cellular interactions and biochemical processes that orchestrate its distinctive clinical manifestation. In the affected skin tissue, a multifaceted interaction between genetic factors, hormonal factors, photoexposure and changes in the extracellular matrix engenders a cascade of events that culminate in the hyperpigmentation characteristic of this condition.^{1,2}

At the molecular level, an underlying genetic contribution to the development of melasma has been identified, where certain genetic variants may predispose to the onset of the condition. In particular, polymorphisms in genes related to melanin production and regulation, such as the MC1R gene and genes involved in the melanocortin signaling pathway, have been investigated in the context of melasma. These genetic variations may influence the response of melanocytes to hormonal and environmental stimuli, exacerbating melanin production and distribution in the epidermis.²

The hormonal component also plays an essential role in the genesis of melasma, with a bidirectional relationship between reproductive hormones and cutaneous melanocytes. Hormonal stimulation, especially melanocyte-stimulating hormone (MSH) and estrogens, can enhance melanocyte activity and stimulate melanin production. These effects are accentuated in the most sun-exposed areas of the skin and may be exacerbated by chronic photoexposure.

The molecular enigma of melasma also extends to the realm of the extracellular matrix, where interactions between epidermal cells, dermal fibroblasts and matrix components create a microenvironment conducive to melanocyte activation and proliferation. Cytokines and growth factors released in response to hormonal stimuli and sun damage can modify skin homeostasis, providing a favorable environment for hyperpigmentation.^{2,3}

In addition, chronic exposure to ultraviolet (UV) radiation and the formation of sun-induced free radicals generate an oxidative environment in the skin, which in turn can stimulate melanin production. Activation of the MITF (microphthalmia transcription factor) transcription factor signaling cascade in melanocytes, following stimuli such as UV radiation and hormones, amplifies melanin production and promotes its accumulation in the epidermis.^{3,4}

In conclusion, an in-depth exploration of the molecular aspects of melasma reveals an intricate network of genetic, hormonal and photoinduced interactions that converge in the characteristic cutaneous hyperpigmentation. Understanding these underlying molecular pathways not only informs the pathogenesis of this condition, but also suggests potential approaches for future targeted therapies that specifically address the molecular alterations involved in the genesis of melasma.¹⁻⁴

RELEVANCE

The prevalence of melasma, a dermatologic condition characterized by acquired cutaneous hyperpigmentation, stands out as an inescapable clinical and epidemiologic concern in contemporary dermatologic health. While the precise magnitude of its prevalence may vary according to geography, ethnic groups and research parameters, epidemiological studies suggest that melasma stands as a widely recognized and globally disseminated skin health problem.^{2,3}

This condition presents a preponderant prevalence in women of reproductive age, often worsening during pregnancy due to inherent hormonal alterations. Furthermore, its wide ethnic distribution reinforces its epidemiological importance, as a higher prevalence has been observed in populations with higher melanin content, particularly in individuals of Asian, Hispanic and Indian subcontinent origin. However, it is crucial to emphasize that melasma is not limited to specific ethnic groups and can manifest in any race, although its presentation may vary.^{3,4}

The clinical relevance of melasma is not only limited to aesthetic considerations, but also permeates psychological and socioemotional aspects. The facial nature of hyperpigmentation can profoundly impact the self-image and self-esteem of affected individuals, affecting their quality of life and emotional well-being. In addition, the recurrence and chronicity of melasma can result in a continuous search for treatment and medical consultations, which entails both financial and time costs for patients.⁴

From a medical perspective, the importance of melasma lies in the need for a thorough understanding of its multifactorial pathogenesis to facilitate effective diagnostic and treatment strategies. Since melasma can be triggered or exacerbated by a variety of factors, such as sun exposure, hormonal changes and genetic predisposition, its therapeutic management requires a personalized and holistic approach. In this context, continued research and innovation in targeted therapies are essential to address this complex dermatological condition more efficiently and successfully.⁴

The widespread prevalence and clinical and emotional impacts of melasma corroborate its medical and social relevance. This article is intended as an effort toward the comprehensive elucidation and appreciation of the nature and importance of melasma, with the aspiration of fostering more comprehensive clinical care and the advancement of more effective therapeutic strategies for the benefit of patients afflicted with this skin condition.⁴

CLINIC

The clinical manifestation of melasma, a complex skin pigmentation disorder, reveals a rich and heterogeneous range of phenotypic features that pose a diagnostic and therapeutic challenge for dermatologic health care

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professionals. The clinical presentation varies markedly according to anatomic location, type of melasma, and environmental and hormonal influences, resulting in a wide diversity of morphologic features that embody spectrums of coloration, texture, and distribution.⁵

Melasma exhibits a predilection for photoexposed areas, such as the face, especially the forehead, cheeks and upper lip, as well as the mandibular region. Three main clinical patterns are distinguished: epidermal melasma, characterized by superficial hyperpigmentation and light brown color; dermal melasma, which exhibits deeper pigmentation and bluish tones; and mixed melasma, an amalgam of both patterns. In addition, a less common form, indeterminate melasma, is recognized, where histopathologic and clinical features cannot be definitively attributed to any pattern.^{5,6}

Differential diagnosis is imperative, as the clinical presentations of melasma can mimic other skin hyperpigmentation conditions, such as postinflammatory dermatitis, postinflammatory hyperpigmentation and lentiginosities. Comprehensive evaluation involves meticulous anamnesis, clinical evaluation and consideration of predisposing and triggering factors. The use of tools such as Wood's light and ultraviolet photography can help reveal the extent and depth of pigmentation, facilitating a more accurate diagnosis.^{6,7}

In this context, the importance of clinical evaluation lies in its influence on the choice of optimal therapeutic strategies. The clinical diversity and recurrence of melasma make an individualized, multifaceted approach to treatment imperative. Therapeutic options range from topical approaches, including depigmenting agents and sunscreens, to more invasive procedures such as laser therapy and chemical peels. The choice of therapy is based on clinical presentation, duration of symptoms and previous response to treatment.⁷

In summary, the clinical manifestation of melasma encompasses a diverse spectrum of phenotypic features, the comprehensive analysis of which is essential for accurate diagnosis and treatment. Understanding clinical variations, considering differential diagnoses and applying personalized therapeutic approaches are essential aspects in the successful management of this challenging dermatologic condition. This article is intended as a compendium that illuminates the varied clinical manifestations of melasma in order to guide health care professionals in optimizing the care of patients affected by this complex skin entity.^{7,8}

DIAGNOSIS

The diagnosis of melasma, an intricate skin condition characterized by acquired hyperpigmentation, demands a meticulous amalgam of clinical evaluation, anamnestic consideration, and a thorough analysis of morphologic and distributional features. Because the presentation of melasma can often mimic other cutaneous pigmentary pathologies,

clinical skill and attention to minute detail are essential to confidently differentiate this entity from other similar conditions.^{8,9}

The anamnesis should inquire in depth about the duration, evolution and circumstances associated with hyperpigmentation. A thorough analysis of triggering and aggravating factors, such as excessive sun exposure, hormonal changes, history of hormonal contraceptive use, as well as previous therapies and history of cosmetic products used, is also required. In addition, the medical history and physical examination should identify comorbidities that could influence the presentation of melasma, such as endocrine disorders, medications and concomitant dermatologic conditions.^{8,9}

Clinical evaluation includes a meticulous assessment of the morphologic features and distribution of hyperpigmentation. Wood's light and ultraviolet photography, useful diagnostic tools, can reveal the extent and depth of pigmentation, as well as the areas affected to varying degrees. Clinical classification according to epidermal, dermal, mixed or indeterminate patterns provides a basis for interpretation of the severity and type of melasma.^{8,9}

The differential diagnosis should address conditions that resemble each other in their clinical presentation, such as postinflammatory hyperpigmentation, solar lentiginosities, and melanocytic neoplasms. Selective skin biopsies, although not routine, may be considered in ambiguous or refractory cases to confirm the diagnosis by histologic observation of the epidermis and dermis.^{9,10}

The application of imaging technologies, such as digital photography and ultraviolet light assessment, can provide quantitative and qualitative analysis of pigmentation, allowing objective monitoring of therapeutic response. Assessment of response to therapeutic modalities plays an integral role in diagnostic confirmation, as an obvious improvement in pigmentation is indicative of melasma.¹⁰

In sum, the diagnosis of melasma involves a meticulous concatenation of anamnesis, clinical evaluation and consideration of differential diagnoses. Understanding the etiologic factors and phenotypic presentation of melasma, together with the use of advanced diagnostic technologies, converges in the accurate confirmation of this cutaneous entity. This article aims to enrich the medical understanding of melasma diagnosis and to provide effective clinical tools to identify and treat this complex pigmentary condition.^{10,11}

TREATMENT

The therapeutic approach to melasma, a dermatologic condition of acquired cutaneous hyperpigmentation, demands a deliberate and contextualized consideration of multiple contributing factors including clinical severity, pigmentation patterns, underlying etiologic factors, and previous response to treatment. Given the chronic and recurrent nature of melasma, therapeutic strategies must be individualized,

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multifaceted and sustained over time in order to achieve effective attenuation of hyperpigmentation and successful management of patient well-being.^{11,12}

In the spectrum of topical interventions, depigmenting agents, such as hydroquinone, kojic acid, azelaic acid and retinoids, stand as fundamental pillars in the treatment of melasma. Their mechanism of action lies in the inhibition of melanogenesis, triggering the gradual reduction of pigmentation. The combination of these agents can enhance their effects and reduce the risk of adverse effects.¹²

Photoprotection is a non-negotiable element in the therapeutic arsenal, as sun exposure plays a major role in the pathogenesis of melasma. Regular use of broad-spectrum sunscreens with high UVA/UVB protection not only minimizes existing pigmentation, but also prevents its recurrence and aggravation. Photoprotection is particularly crucial during depigmenting treatment to avoid stimulation of melanogenesis by ultraviolet radiation.¹³

For refractory cases or those with a more severe presentation, dermatologic procedures such as chemical peels and laser therapy offer valuable alternatives. Chemical peels with glycolic acid, salicylic acid or trichloroacetic acid can exfoliate the superficial layer of the skin, eliminating hyperpigmentation and stimulating regeneration of the epidermis. Laser therapy, in its various modalities, such as Q-switched Nd:YAG and fractional lasers, acts at the dermal level, fragmenting melanin granules and stimulating cell renewal.¹⁴

It is essential to emphasize that successful management of melasma is not just about treatment per se, but also encompasses patient education about the chronic nature of the condition, the need for ongoing therapeutic adherence, and commitment to preventive measures such as photoprotection. Multidisciplinary management, involving dermatologists, endocrinologists and mental health professionals, can provide comprehensive and integrated care that considers medical, aesthetic and emotional aspects.^{15,16}

The treatment of melasma goes beyond the application of isolated therapeutic modalities and requires a strategy that adheres to the principle of individualization. Consideration of clinical, etiologic and response factors, along with the implementation of preventive measures and patient education, is at the core of the rigorous and holistic medical approach proposed in this article.^{17,18}

CONCLUSIONS

Melasma, a multifaceted and challenging dermatologic entity in nature, stands as a fertile field for medical research and clinical care. Through in-depth and detailed analysis of its pathogenesis, clinical presentation, diagnosis, and therapeutic approaches, this article has delineated the wealth of existing knowledge and strategies that allow for a deeper understanding and more efficient management of melasma.

Exposure of the complex interactions between genetic, hormonal, environmental factors and excessive sun exposure has unraveled the underlying etiologic basis of melasma. Appreciation of its varied clinical manifestations and meticulous consideration of differential diagnoses has culminated in a more precise and accurate diagnostic approach. The comprehensive exploration of therapeutic strategies, including topical options, photoprotection and advanced dermatologic procedures, has shed light on the need for personalized, multidisciplinary approaches that address the medical, aesthetic and psychosocial aspects of melasma. While this article has succeeded in providing a comprehensive overview of the medical and clinical aspects of melasma, the picture still presents areas of uncertainty and opportunities for future research. The identification of predictive biomarkers of therapeutic response, the exploration of new depigmenting agents, and the development of more effective preventive strategies emerge as promising directions. In addition, the need for studies that evaluate the long-term efficacy and safety of existing therapies, especially in diversified populations, remains an imperative in the search for more optimal therapeutic approaches.

Ultimately, the opening of Pandora's box regarding melasma has fostered a greater understanding of its mysteries and complexities, while reaffirming the importance of comprehensive, patient-centered medical care. Confronting the clinical and scientific challenges inherent in melasma not only enriches knowledge in dermatology, but also redoubles the commitment of health care professionals to improve the quality of life of affected patients. This article aspires to serve as a milestone on the road to a more refined and effective approach to understanding and addressing melasma, igniting the flame of continued inquiry and clinical excellence in this fascinating dermatologic sphere.

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