# Melasma : Current Insight into Its Etiology and Diagnosis Approaches

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**Abstract**

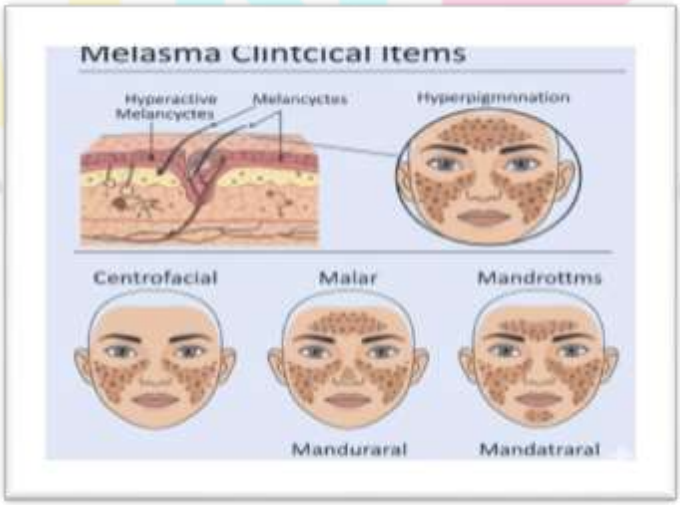
Melasma is a chronic, acquired hypermelanosis disorder characterized by irregular brown to gray-brown macules and patches, predominantly affecting sun-exposed facial regions such as the forehead, cheeks, nose, upper lip, and chin. It is more common in women of reproductive age, particularly in individuals with Fitzpatrick skin types III–V, and is associated with significant psychosocial distress. The etiology of melasma is multifactorial, with strong contributions from genetic predisposition, hormonal influences, ultraviolet (UV) radiation, cosmetics, phototoxic agents, and certain medications. Hormonal fluctuations during pregnancy, oral contraceptive use, and hormone replacement therapy are major triggers that enhance melanocyte activity through estrogen, progesterone, and melanocyte-stimulating hormone (MSH) pathways. The pathophysiology of melasma involves a complex interplay of molecular pathways including upregulation of tyrosinase, activation of MC1R receptors, Wnt/β-catenin signaling, endothelin-1 pathways, fibroblast-derived growth factors, oxidative stress mechanisms, and inflammatory cytokines. Diagnosis is primarily clinical, supported by complementary tools such as Wood's lamp examination, dermoscopy, reflectance confocal microscopy (RCM), immunohistochemistry, hormonal assays, and histopathology. These diagnostic methods help determine the depth of pigmentation, classify melasma into epidermal, dermal, or mixed types, and guide treatment planning. While clinical examination remains the cornerstone due to its simplicity and accessibility, advanced imaging techniques like RCM provide near-histologic resolution and enhance diagnostic precision. Understanding the etiological factors and diagnostic modalities is essential for accurate assessment and effective management of melasma.

**Keywords:** Melasma; Hyperpigmentation; Dermoscopy; Wood's lamp; Reflectance confocal microscopy; Tyrosinase; UV radiation; Hormonal influence; Pathophysiology; Diagnosis.

## 1. Introduction

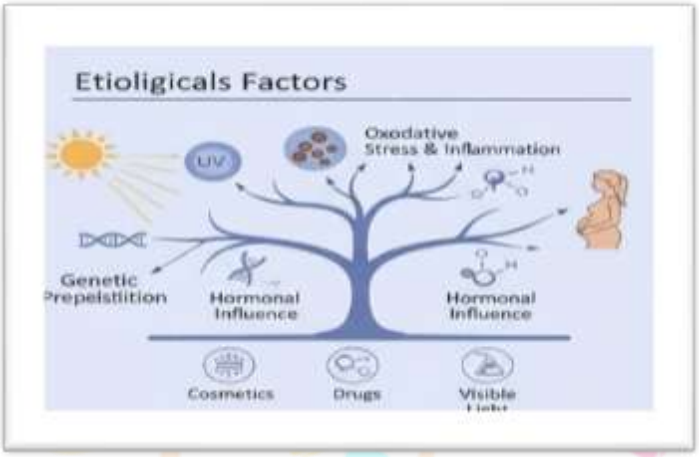
Melasma is a chronic, acquired disorder of hyper melanosis that manifests as irregular, brown, or Gray-brown macules and patches, primarily on the face particularly the forehead, cheeks, nose, upper lip, and chin. It predominantly affects females of childbearing age but is also observed in males and individuals of diverse ethnicities [1,2]. Melasma can have a significant psychosocial impact, often affecting self-esteem and quality of life, particularly in individuals with darker skin tones (Fitzpatrick types III–V). Based on histopathology, it is categorized into three types: epidermal, dermal, and mixed [3,4,5].

Clinically, melasma is a diagnosis of observation, characterized by well-defined hyperpigmented macules and patches. It may be further classified according to facial distribution as Centro facial, malar, or mandibular types.



**2. Etiological Factors**

The exact etiology of melasma remains unclear; however, it results from a complex interaction between genetic, hormonal, and environmental factors that increase melanin synthesis and melanocyte activity.




**2.1 Genetic and Hereditary Factors**
Up to 33–50% of melasma patients report a positive family history, suggesting a strong genetic predisposition. Twin studies also confirm a hereditary influence [6].

**2.2 Hormonal Influence and Pregnancy**
Hormonal changes, especially during pregnancy (often termed the "mask of pregnancy"), play a vital role. Elevated estrogen, progesterone, and melanocyte-stimulating hormone (MSH) stimulate melanogenesis. Melasma is also seen in women using oral contraceptive pills and in postmenopausal women receiving hormone replacement therapy [8].

**2.3 Sun Exposure**
Ultraviolet (UV) and visible light exposure are major triggers. UVA and UVB rays induce oxidative stress and lipid peroxidation, leading to increased melanin synthesis through the activation of melanocytes and inflammatory mediators.

**2.4 Cosmetics and Phototoxic Agents**
Certain cosmetic products and topical agents can cause phototoxic or photoallergic reactions, worsening pigmentation.

**2.5 Drugs**
Some medications, including anticonvulsants (e.g., clobazam), nonsteroidal anti-inflammatory drugs, antibiotics, retinoids, and psychotropic drugs, are known to induce or exacerbate melasma-like pigmentation.

**3. Pathophysiology**

| Molecular Pathway | Role in Melasma Pathophysiology | Effect on Pigmentation |
|---|---|---|
| Tyrosinase Activity | Tyrosinase is the rate-limiting enzyme in melanin synthesis | Increased melanin production |
| Melanocortin 1 Receptor (MC1R) | Receptor for melanocyte-stimulating hormone (MSH) | Stimulates melanogenesis and melanocyte proliferation |
| Estrogen and Progesterone Receptors | Hormonal signals increase melanocyte activity | Hormone-induced hyperpigmentation |

| | | |
|---|---|---|
| Wnt/β-catenin Pathway | Regulates melanocyte differentiation and survival | Enhances melanocyte proliferation and pigment synthesis |
| Endothelin-1 Pathway | Released from keratinocytes and endothelial cells, stimulates melanocytes | Promotes melanocyte activation |
| Oxidative Stress Pathways | UV-induced reactive oxygen species lead to melanocyte activation | Triggers increased melanin synthesis |
| Fibroblast Growth Factor (FGF) | Dermal fibroblasts secrete FGF influencing melanocyte behavior | Promotes melanogenesis and pigmentation persistence |
| Inflammatory Cytokines (e.g. IL-1, TNF-α) | Inflammation-mediated activation of melanocytes | Sustains melanocyte stimulation and pigmentation |

**4.Diagnosis**

Melasma is primarily diagnosed by clinical examination, but several non-invasive and laboratory-based tools help confirm its type, determine pigment depth, and differentiate it from other pigmentation disorders. A combination of these techniques provides the most accurate assessment for both diagnosis and treatment monitoring [10,11].

**4.1Clinical Examination**

The first and most essential step in diagnosing melasma is clinical observation. Dermatologists identify melasma by its typical features symmetrical brown to Gray-brown macules and patches on sun-exposed parts of the face such as the cheeks, forehead, upper lip, and chin [14,15]. Clinical examination is the cornerstone for diagnosing melasma, involving assessment of characteristic skin changes, risk factors, and relevant history. Diagnosis is fundamentally clinical, based on the appearance, pattern, and distribution of hyperpigmentation on the face, complemented by adjunctive tools such as Wood lamp and dermoscopy for subtype classification and differentiation from other pigmentary disorders.

- **Advantages**

**Non-Invasive and Quick:** Does not require laboratory tests or tissue samples, allowing easy, immediate diagnosis in an outpatient setting.
**Cost Effective:** Involves no expensive equipment or consumables unless Wood lamp or dermoscopy is used.
**Widely Accessible:** Can be performed by any trained healthcare provider without specialized resources.
**Direct Assessment:** Enables rapid differentiation from other pigmentary disorders and assessment of severity (using tools like MASI or mMASI).

- **Disadvantages**

**Subjectivity:** Dependent on the clinician's experience, which may introduce inter-observer variability, especially in mild or atypical cases.
**Limited Depth Assessment:** Cannot reliably distinguish between epidermal, dermal, or mixed types of melasma without adjunct tools.
**Overlap with Mimickers:** Some presentations may resemble other pigmentary disorders, leading to diagnostic uncertainty in certain cases.
Cannot determine the depth of pigmentation (epidermal or dermal).
May be confused with other conditions such as post-inflammatory pigmentation or drug-induced pigmentation.

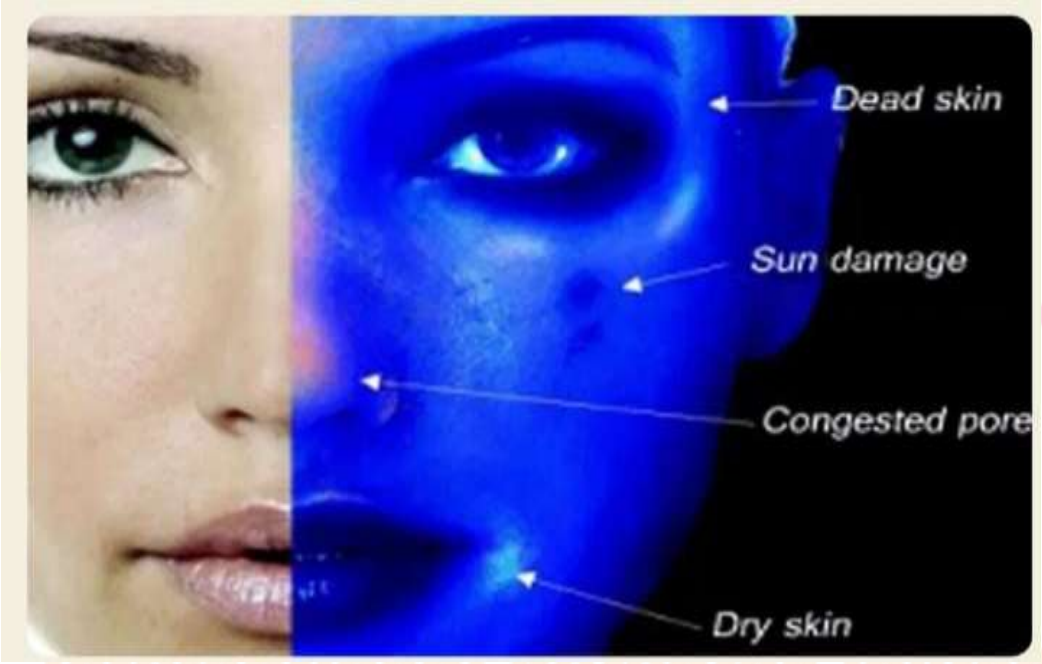
- **Limitations**

**Variable Presentation:** Skin phototype, lesion site, and chronicity may complicate the assessment.
**Adjunct Tools May Be Needed:** For subtyping or atypical presentations, tools like Wood lamp, dermoscopy, or even histopathology may become necessary.

**Measurement Challenges:** Assigning severity or monitoring treatment may require validated scoring systems (e.g., MASI), which themselves have subjective elements.

**4.2 Wood's Lamp Examination**

Wood's lamp examination is a simple, non-invasive diagnostic tool that can help in assessing melasma, particularly in individuals with lighter skin types. Under ultraviolet (UV) light (wavelength ~365 nm), epidermal melasma appears more accentuated or darker because the excess melanin in the basal and suprabasal layers of the epidermis absorbs the light. In contrast, dermal melasma does not show enhancement under Wood's lamp, as the melanin is located deeper in the dermis, beyond the reach of UV light. When lesions exhibit both enhancing and non-enhancing areas, they are classified as mixed-type melasma [18,19].
However, it is important to note that the accuracy of Wood's lamp in differentiating between epidermal and dermal melasma is limited. A histopathological study revealed that even in cases appearing epidermal under Wood's light, increased melanin was found in both the epidermis and dermis. This suggests that many cases are actually mixed-type melasma, regardless of Wood's lamp findings. Therefore, while useful as an initial diagnostic aid, Wood's lamp examination should be interpreted with caution and ideally complemented with other diagnostic methods such as dermoscopy or histopathology [20,21].
Wood's lamp emits ultraviolet (UV) light (320–400 nm) to examine skin fluorescence. It helps classify melasma based on pigment depth:




- **Advantages**

**Non-Invasive and Quick:** No skin sampling or discomfort for the patient, making it suitable for routine use.
**Guides Treatment:** Helps classify the depth of pigmentation, which is important for selecting appropriate therapies—epidermal melasma responds better to topical treatments.
**Cost Effective:** Inexpensive and accessible for most dermatology practices.
**Immediate Results:** On-the-spot evaluation enhances patient counseling and decision-making.

- **Disadvantages**

**Limited Sensitivity and Specificity:** Studies show only moderate sensitivity and accuracy (about 46%) in correctly classifying melasma types; results can be misleading, especially with mixed or dermal melasma.
**Subjectivity:** Interpretation relies on clinician experience and ambient light conditions; error rates vary.
**Inconsistent with Skin Types:** Lower reliability in patients with darker skin (high phototypes) due to poor contrast under UV light.
**Cannot Replace Other Modalities:** Does not match the diagnostic precision of histopathology or advanced imaging (like reflectance confocal microscopy).

- **Limitations**

**Overlap of Findings:** Mixed types are hard to classify clearly; dermal pigment changes may remain invisible under the lamp.
**Environmental Factors:** Performance can be affected by the presence of sunscreen, makeup or skin products.
**Low Concordance with Histopathology:** Comparative studies indicate discordance between Wood's lamp results and histological findings especially in dermal and mixed melasma.
**Adjunct not Standalone:** Should be used together with clinical examination and possibly dermoscopy for better diagnostic accuracy.

**4. 3 Dermo-scopy**

Dermoscopy serves as a valuable, non-invasive technique for evaluating melasma. Under dermoscopic examination, areas of pronounced hyperpigmentation are typically visible along the pseudoridges of the skin. The intensity and pattern of pigmentation help in determining both the concentration and depth of melanin within the skin. When melanin is confined to the stratum corneum or upper epidermal layers, it usually appears as a well-defined, dark brown pigment network. In contrast, melanin located in the lower epidermal layers produces a lighter brown and more irregular network [25,26]. When melanin is situated deeper in the dermis, it takes on a bluish or blue-Gray appearance, due to the scattering of light within the dermal tissue (Tyndall effect). Thus, dermoscopy provides important clues for differentiating between epidermal and dermal pigmentation, aiding in the clinical classification and management of melasma [28,29].
Dermoscopy (epiluminescence microscopy) magnifies the skin (6×–400×) to visualize pigmentation patterns and vascular structures.

- **Advantages**

Non-Invasive and Objective: No discomfort, quick procedure, and provides objective assessment of pigment colour and distribution.
Subtype Classification: Superior to Wood's lamp for determining melasma depth; less affected by skin type, topical products, or vascular changes.
Monitoring Tool: Useful for assessing treatment response and for early detection of complications such as telangiectasia or exogenous ochronosis.
Differential Diagnosis: Helps distinguish melasma from other facial hyperpigmentation (e.g., lichen planus pigmentosus, exogenous ochronosis), may assist biopsy site selection if needed.

- **Disadvantages**

Requires Training: Interpretation is dependent on clinician's experience and skill with pattern recognition.
Limited Accessibility: Dermoscopic devices may not be available in all clinical settings, though increasingly commonplace.
Subjectivity: Some elements of pattern recognition may remain subjective, leading to inter-observer variability.

- **Limitations**

Cannot Definitively Diagnose: Adds clarity but does not replace histopathology in ambiguous or atypical cases.
Single-Site Assessment: Only assesses the site examined; may not represent disease variability across the face.
Potential Overlaps: Certain dermoscopic features may overlap with other pigmentary disorders, requiring clinical correlation..

**4.4 Reflectance Confocal Microscopy (RCM)**

RCM is a high-resolution, non-invasive imaging technique that visualizes skin layers at near-histologic detail using laser light. Reflectance Confocal Microscopy (RCM) is a cutting-edge, non-invasive imaging technique that enables real-time, cellular-level analysis of the skin making it highly valuable for melasma diagnosis, subtyping, and treatment monitoring [31,32].

RCM provides images comparable to histopathology without tissue removal, mapping pigment and cellular changes with high sensitivity.

- **Advantages**

Non-Invasive and Painless: No biopsy or skin preparation is required, and it is well-tolerated by patients.
High-Resolution Imaging: Provides near-histological, cellular-level visualization for pigment mapping, melanocyte activity, and dermal changes.
Objective Subtyping: Offers superior accuracy for classifying melasma as epidermal, dermal, or mixed, outperforming Wood's lamp and often correlates with histopathology findings.
Monitoring Tool: Allows dynamic assessment of treatment response and cellular alterations, useful for evaluating efficacy of therapies.
Guides Therapy: Precise pigment and cell mapping inform individualized therapeutic strategies.

- **Disadvantages**

**Cost and Accessibility:** RCM devices are expensive and not widely available in general clinics; require specialized infrastructure.
**Technical Demand:** Image interpretation demands significant training and expertise, with a risk of inter-observer variability.
**Limited Depth:** Only assesses the epidermis and superficial dermis, so deeper dermal changes may be missed.
**Time Intensive:** Each exam may require more time compared to simpler methods like Wood's lamp.

- **Limitations**

Availability: Limited to specialized centers, restricting broader clinical use for diagnosis and routine management.
Single-Area Assessment: Examines only selected skin areas, which may not represent disease heterogeneity across the face.
Cannot Replace Clinical or Histology: Best used as an adjunct; sometimes further evaluation or biopsy is required in unclear cases.
Requires Training: Experienced operators are needed for accurate interpretation and reproducibility.

**4.5 Immunohistochemistry (IHC)**

Immunohistochemistry (IHC) is a vital diagnostic tool in dermatopathology and is sometimes used in the investigation of melasma, primarily for research and advanced diagnosis to understand the underlying pathogenesis of the disorder. While melasma is primarily diagnosed clinically and through histopathology, IHC can help assess the distribution and activity of melanocytes, expression of melanogenic markers, and other relevant proteins in affected and unaffected skin to provide deeper insights into disease mechanisms [35,36,37].

- **Advantages**

**Specificity and Sensitivity:** Allows for highly specific detection of various cell types and proteins implicated in melasma, even within complex tissue contexts.
**Spatial Resolution:** Preserves tissue architecture, enabling precise localization of proteins in the epidermis and dermis, which is valuable in differentiating epidermal and dermal subtypes of melasma.
**Research Utility:** Useful in identifying molecular pathways, inflammatory mediators, and the distribution of pigment and related markers not visible with routine stains.
**Applicability:** Can be used on standard, formalin-fixed, paraffin-embedded tissue, making it compatible with most biopsy samples.

- **Disadvantages**

**Not Routinely Required:** IHC is usually not necessary for the routine diagnosis of melasma, which is typically made clinically or with standard histology.
**Interpretation Challenges:** Results can be subjective and require significant expertise, leading to potential inconsistencies between observers.
**False Positives/Negatives:** Non-specific staining and technical issues may result in misleading findings if not properly controlled.
**Cost and Labor Intensive:** The procedure is time-consuming and more expensive than standard stains, limiting its use primarily to research and complex diagnostic scenarios.

- **Limitations**

**Standardization Issues:** Variability in antibody quality, staining protocols, and interpretation may affect reproducibility between laboratories.
**Limited Diagnostic Value:** Does not distinguish melasma from other hyperpigmentation disorders in most cases, as findings may overlap with other pigmentary conditions.
**Not a Standalone Test:** Should always be interpreted alongside clinical findings and standard histology for accurate diagnosis.

**4.6 Hormonal Assay**

Hormonal assay is an investigative test used to measure hormone levels in the blood, which can help assess the role of hormones in the development and persistence of melasma. While not a routine diagnostic test for melasma, hormonal assays are mainly utilized in research and select cases to understand underlying risk factors, especially in atypical presentations or when hormonal disorders are suspected.
Because melasma often has hormonal associations, blood assays measuring FSH, LH, MSH, progesterone, prolactin, and TSH may support diagnosis .

- **Advantages**

**Insight Into Etiology:** Offers comprehensive information about the role of hormones in triggering and maintaining melasma, which is especially useful in cases associated with pregnancy, oral contraceptives, or hormone therapy.
**Guidance for Management:** Helps inform treatment decisions, such as discontinuing hormone therapy or managing underlying endocrine disorders.
**Personalized Approach:** Identifies individual risk factors, allowing for tailored interventions, particularly in patients with persistent or recurrent melasma.
**Research Utility:** Valuable for epidemiological studies and understanding pathogenesis on a molecular level.

- **Disadvantages**

**Limited Diagnostic Value:** Melasma is primarily diagnosed clinically; hormonal assay is rarely needed in routine practice and may not change management in the majority of cases.
**Non-Specific Results:** Abnormal hormone levels are not exclusive to melasma and may be found in other conditions, reducing specificity.
**Cost and Accessibility:** Testing is expensive and not widely available in all settings.
**Patient Burden:** Blood sample collection may be inconvenient and cause discomfort.

- **Limitations**

**Variability:** Hormone levels fluctuate throughout the menstrual cycle and with age, making interpretation complex without serial measurements.
**No Direct Diagnosis:** Does not replace clinical evaluation or histopathology for melasma diagnosis; results must be interpreted in conjunction with other findings.
**Overlapping Factors:** A variety of environmental, genetic, and endocrine factors contribute to melasma, so hormonal assays cannot define the condition on their own.

**4.7 Histopathological Examination (Biopsy)**
Histopathological examination (biopsy) provides detailed microscopic insights into melasma, helping identify characteristic features and distinguish its subtypes, although it is reserved for atypical or research cases rather than routine diagnosis. Biopsy allows

evaluation of pigment distribution, cellular changes, and dermal alterations, offering the highest diagnostic precision for melasma pathology.

Skin biopsy is rarely used but provides definitive confirmation of pigment distribution. It shows increased melanin in basal keratinocytes. Presence of dermal melanophages.

- **Advantages**

**Definitive Characterization:** Provides direct, objective visualization of epidermal and dermal pigment, cellular changes, and associated tissue alterations.
**Subtype Confirmation:** Accurately differentiates epidermal, dermal, and mixed melasma, especially in clinically ambiguous cases.
**Reveals Pathogenic Clues:** Identifies chronic sun damage (solar elastosis), increased blood vessels, mast cells, and melanophages, deepening the understanding of melasma's causes.
**Adjunct for Difficult Cases:** Useful when diagnosis is uncertain, or in atypical or therapy-resistant pigmentation.

- **Disadvantages**

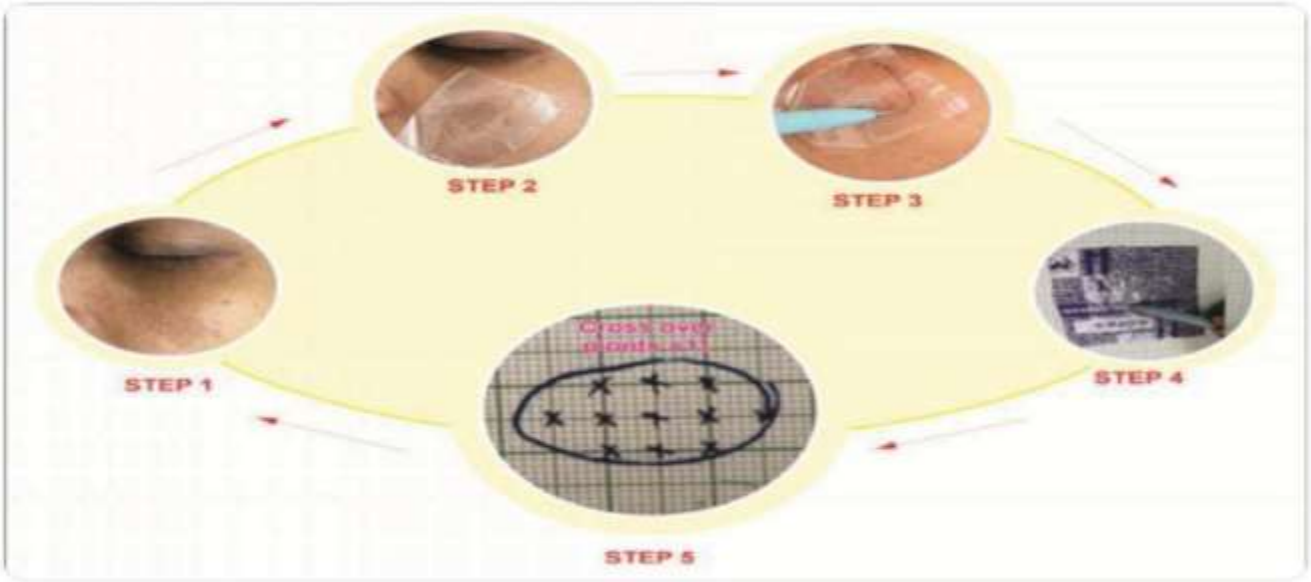
**Invasive Procedure:** Requires local anesthesia and tissue removal, with risk of pain, infection, and potential scar formation—significant drawbacks in cosmetic conditions.
**Not Routinely Needed:** Diagnosis of melasma is usually clinical; biopsy is only indicated if there is doubt about the diagnosis or malignancy is suspected.
**Patient Reluctance:** Cosmetic concerns and the risk of scarring limit patient acceptance.
**Cost and Infrastructure:** More resource-intensive than noninvasive approaches.

- **Limitations**

Single-Site Assessment: Only a small area is examined, which may not represent the full spectrum of disease.
Limited Correlation with Severity: Histological findings (such as pigment depth or number of melanocytes) do not always correlate with clinical severity or the Melasma Area Severity Index (MASI).
Cosmetic Complications: Even small biopsies may leave visible marks on cosmetically sensitive areas like the face.
Research-Oriented: Primarily reserved for research or unresolved, atypical cases.

**4.8Melasma Area and Severity Index (MASI)**

The MASI (Melasma Area and Severity Index) test is a commonly used clinical tool for assessing the severity of melasma, especially in research and clinical trials. The MASI score takes into account both the area of involvement and the intensity of pigmentation in four facial regions: forehead, right malar, left malar, and chin. The original MASI formula calculates severity using scores for the affected area (from 0 to 6), darkness (from 0 to 4), and sometimes homogeneity (also 0 to 4, though later removed for simplicity). The final MASI score ranges from 0 (no involvement) to 48 (most severe involvement).




**How the MASI Index Is Calculated**

- **Area (A)**: Each region of the face is scored for the percentage of involvement (0 = 0%, 1 = <10%, 2 = 10-29%, 3 = 30-49%, 4 = 50-69%, 5 = 70-89%, 6 = 90-100%).
- **Darkness (D)**: Each region receives a score for darkness (0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe).
- **Homogeneity (H)**: Originally included, scored 0 to 4, but this was later excluded in the modified MASI (m-MASI).
- **Calculation**: The MASI score uses the formula:

$$\text{MASI} = 0.3 \times (A_f \times D_f) + 0.3 \times (A_{rm} \times D_{rm}) + 0.3 \times (A_{lm} \times D_{lm}) + 0.1 \times (A_c \times D_c)$$

Where:

- $A_f, D_f$: Forehead area and darkness
- $A_{rm}, D_{rm}$: Right malar area and darkness
- $A_{lm}, D_{lm}$: Left malar area and darkness
- $A_c, D_c$: Chin area and darkness

- **Advantages**

MASI is widely accepted and used in clinical research, providing a standard method for quantifying melasma severity and monitoring response to treatments.
It allows objective tracking of disease progression or improvement by scoring area and darkness of pigmentation in different facial regions.
MASI is clinically practical, does not require specialized equipment, and is relatively easy to apply, especially in research settings.

- **Disadvantages**

The MASI formula can be subjective, especially regarding area estimation and pigmentation assessment, leading to potential inter-rater variability.
It is moderately complex and time-consuming which may hinder its use in busy clinical settings and requires training for consistency.
The method tends to give an overemphasis to area size rather than the intensity of pigmentation, which can misrepresent actual severity in some cases.

- **Limitations**

MASI's subjectivity and reliance on visual scoring reduce reproducibility, with moderate inter-rater reliability compared to more objective or digitally-assisted methods.
It does not adequately address variations in pigmentation intensity across different facial zones, notably the nose, which can affect scoring accuracy.

**5.Conclusion**

Accurate diagnosis of melasma relies on combining clinical evaluation with objective diagnostic tools to determine pigment depth and pathogenesis.
While clinical and Wood's lamp examinations remain the mainstay in practice, dermoscopy and RCM provide enhanced visualization, and IHC and hormonal assays help in understanding underlying mechanisms.
Each technique has distinct advantages and limitations; hence, an integrated diagnostic approach ensures precise classification and effective management of melasma .
Melasma is a complex, multifactorial pigmentation disorder with significant psychosocial impact. Although clinical evaluation remains the mainstay of diagnosis, adjunct tools such as Wood's lamp, dermoscopy , and reflectance confocal microscopy improve diagnostic accuracy. Early recognition and identification of contributing factors are essential for effective management and prevention of recurrence. Continued research into hormonal, genetic, and vascular pathways may lead to more targeted and long-lasting therapeutic options.

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