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Review Article

Latin American consensus on the treatment of melasma

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Abstract

Melasma is a chronic, relapsing hyperpigmentation disorder that primarily affects photoexposed areas, occurring most frequently in adult women with darker skin phototypes. The primary factors contributing to its development include sun exposure, sex hormones (e.g., pregnancy), and genetic predisposition. Melasma is highly prevalent in Latin America, where many countries lie in intertropical zones and exhibit significant ethnic diversity because of centuries of intermixing among Native Americans, Europeans, and Sub-Saharan Africans. Nine Latin American experts formulated a DELPHI-based consensus to develop a valuable approach for treating melasma in this diverse population. After establishing an accurate diagnosis, assessing the impact on quality of life, and determining disease severity, the consensus recommends mitigating known triggers and promoting rigorous photoprotection. Active therapy should be tailored based on individual characteristics (e.g., pregnancy status, previous treatments, skin sensitivity). Treatment options include topical depigmenting agents, systemic therapies, and procedural interventions such as laser therapy, microneedling, and chemical peels. Periodic reassessment of the treatment is essential, with strategies adjusted if targeted outcomes are not achieved. Once clinical remission is attained, patients should continue using topical depigmenting agents and maintain strict photoprotection measures to prevent recurrence.

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Introduction

Melasma is a chronic acquired and relapsing hyperpigmentation disorder characterized by significant dysfunction in melanogenesis because of complex interactions between the epidermis and dermis involving multiple cell types. Ultraviolet light (UV) exposure impacts the epidermis and upper dermis, triggering the production of various mediators of dermal inflammation, endothelial proliferation, fibrosis activation, and increased melanogenesis,[1,2] among other factors.[3,4]

Melasma diagnosis relies on its clinical manifestations (Table 1). It presents as brown patches, especially on the face. The Melasma Area and Severity Index (MASI) is widely used.[5] Supporting diagnostic tools are available.[6–8]

The differential diagnosis of melasma includes several skin conditions involving hyperpigmentation (Table 2).

Quality of life

Despite being asymptomatic, pigmentary disorders can significantly impact the quality of life. Melasma affects appearance and interpersonal relationships.[9,10] Psychometric questionnaires are employed to evaluate this negative impact on the quality of life. Figure 1 summarizes the characteristics of two tools, the Dermatology Life Quality Index (DLQI) and the Melasma Quality of Life Scale (MelaQoL), for assessing patients' quality of life with melasma.

Several factors contributing to a decreased quality of life, as measured by the MelaQoL, include a history of previous treatments for melasma (indicative of recurrence) and a history of mental or mood disorders.[11]

Physiopathology

Melanogenesis is regulated through various signaling networks. Although melasma is clinically characterized by epidermal hyperpigmentation, the histopathological changes affect both the epidermis and upper dermis. Figure 2 outlines the predominant mechanisms involved in the skin changes observed in individuals with melasma.

Epidemiology

Melasma is one of the five most common dermatoses in Mexico and Brazil and a leading cause of dermatological consultation.[1,12–17] However, as Table 3 illustrates, epidemiological data on melasma in Latin America are limited and variable.

According to Cestari et al., the overall prevalence in the Latin American population is 10%.[18] The Brazilian Society of Dermatology conducted a survey in 2024, where the prevalence of facial melasma was 36.3%.[19] Pregnant Latinas have a prevalence between 50% and 80%, a third of them with a chronic form, suggesting that Latino ancestry could be a predictive factor.[16]

The frequency of pigmentation disorders is likely higher in the Latino population.[20]

Table 1 The main characteristics involved in the diagnosis of melasma

Domain	Characteristics
Clinical manifestations	Acquired hyperpigmentation characterized by brown patches with irregular, symmetrical, and generally bilateral borders located in photoexposed areas of the face
Associated symptoms	Mostly asymptomatic. There may be pruritus, tingling, xerosis, redness or telangiectasias
Affected population	Young, adult women, mainly of Asian or Hispanic origin and most frequently in Fitzpatrick skin phototypes III and IV
Anatomical regions where it manifests itself	• Centrofacial pattern: forehead, cheeks, nose, upper lip, and chin • Malar pattern: lateral areas of the cheeks • Mandibular pattern: lower jaw • Extrafacial melasma: at older ages, associated with menopause
Evaluation	MASI and its modifications
Severity	Mild, moderate, or severe
Support for the diagnosis	• Wood lamp examination • Dermoscopy • Confocal microscopy

Leading domains that support the diagnosis, classification, and evaluation of melasma.
MASI, Melasma Area and Severity Index.

In Peru, melasma comprises between 4% and 10% of new dermatology referrals.[21] In Puerto Rico, men accounted for 10% of melasma cases.[22]

Results of three studies evaluating Latino male workers in North Carolina (USA) implied that genetic factors influence the prevalence of the disease.[20]

Associated factors

Exposure to UV radiation is the most critical factor associated with the development of melasma,[3,14] followed in order by others, as illustrated in Figure 3.

Methodology

From September 2023 to May 2024, nine Latin American dermatologists from Argentina, Brazil, Chile, Colombia, Ecuador, El Salvador, Mexico, Nicaragua, and Peru, all with recognized academic careers, clinical practices, and scientific expertise, collaborated to collect and analyze international and Latin American publications on melasma.

The collaboration began with an initial meeting in September 2023. Relevant topics were defined and assigned to experts to identify and review current literature to generate baseline updated information on melasma. In October, experts analyzed the baseline information to specify the final topics for the consensus and agreed upon developing the first draft. In December, the first draft was reviewed. Topics where no unanimous consensus was reached were identified, and questions to settle these controversies were formulated to be solved following the DELPHI methodology through an anonymous survey round.[23] In February 2024, the DELPHI survey results were presented, the second draft of the manuscript was reviewed, and the topics that did not reach at least 75% of participants' agreement were formulated as questions for a second round DELPHI survey. In April, the second DELPHI survey results were presented, the final draft of the manuscript was reviewed, and a plan for the final submission document was accepted. In May 2024, the final submission document was reviewed, and the submission process was planned.

The results reflect the viewpoints unanimously agreed upon by the participating experts. Unsettled issues were considered consensual when at least 75% of participants agreed. Poll distribution for controversial issues not reaching consensus was included in the results where relevant.

Table 2 Foremost differential diagnoses of melasma

Condition	Differential features
Postinflammatory hyperpigmentation	Brown, pink, or red spots with irregular distribution coinciding with an area of previous injury or inflammation
Friction melanosis	Because of chronic irritation in areas of constant friction such as the neck, armpits, or groin
Pigmented lichen planus	Dark brown to black, flat, itchy lesions
Poikiloderma of Civatte	It affects the neck and lower part of the face, causing irregularly distributed redness, telangiectasias, atrophy, and pigmentation
Ephelides	Small, numerous, and typically darker in the summer
Solar lentigo	Well-defined lesions associated with chronic sun exposure in older adults
Riehl's melanosis	Result of contact dermatitis, often related to cosmetics and with a cross-linked pattern
Ochronosis	It can be endogenous (congenital) or exogenous (associated with hydroquinone use); both have blue or black spots
Hori's nevus	Hyperpigmented macules in the periocular area, bilateral and symmetrical, blue-gray in tone
Addison's disease	Endocrine condition, with generalized hyperpigmentation, affects the mucous membranes
Fusca line	Hyperpigmented band of light brown that extends horizontally along the forehead, respecting the hairline
Pigment demarcation lines on the face	A homogeneous, bilateral, well-defined hyperpigmented patch that is located and extends from the lateral orbital edges or corners of the mouth
Maturational pigmentation	It affects temporal and periocular regions in dark-skinned people and is usually associated with insulin resistance

Diverse features of other hyperpigmentation conditions than melasma.

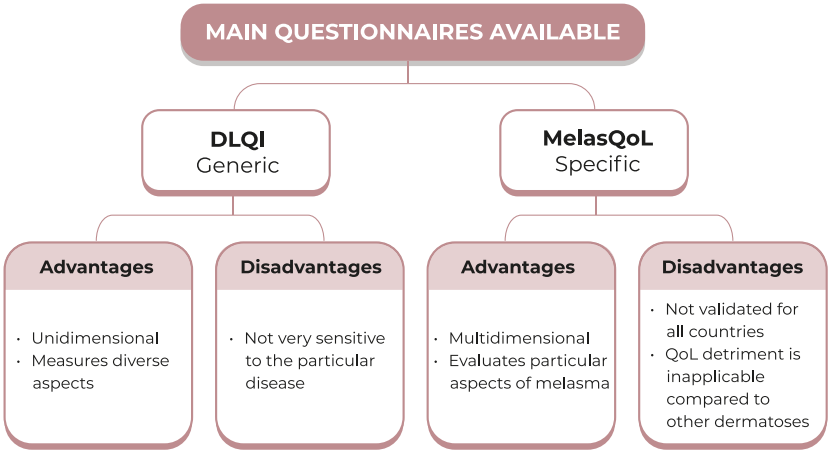

Figure 1 The influence of melasma on patients' quality of life is primarily reflected in emotional distress, expressed by dissatisfaction, frustration, shame, depression related to their skin condition, and feeling "unattractive," affecting their social life[10]

Results and discussion

The baseline reviewed information was summarized in the introduction of this paper.

Melasma is the leading cause of dermatological consultation in Latin America, and its management remains unstandardized because of circumstances such as ethnic diversity across geographical regions.[24–26] As is common in other medical areas,[27] existing treatment guidelines for melasma are based on scientific evidence and incorporate expert opinions to fill evidence gaps. In Latin America, published treatment guidelines include a regional one in 2009[19] and a national one in Mexico (2018),[1] Chile (2021),[28] Peru (2021),[29] and Brazil (2022).[30]

Table 4 lists the unanimous consensus statements and those with a ≥ 75% agreement in the Delphi surveys, and Table 5 lists the differences identified between existing continental guidelines. Topics that did not reach a consensus are indicated in the corresponding section of the discussion. A melasma management algorithm for Latin American countries was developed as part of the consensus.

Treatments

Managing melasma is a challenge demanding a comprehensive understanding of its etiology, triggering factors, and variability in patient response to therapeutic interventions. Factors such as pregnancy, the use of phototoxic drugs, sun exposure patterns, and previous treatment outcomes must be considered. Therapeutic approaches are often combined for optimal results.

Photoprotection

Photoprotection is essential to reducing the incidence and severity of melasma. Appropriate behavior during sun exposure, wearing suitable clothing, and using recommended sunscreens are the mainstays of modern photoprotection (Figure 4).

Since VL also induces pigmentation,[31] a broad-spectrum sunscreen with iron oxide as a VL-absorbing pigment is recommended.[32] Oral antioxidants are considered a complementary treatment to photoprotection.[33]

Topical agents

Topical agents are prevailing elements of melasma treatment. The decision on which agents to use is influenced not only by scientific evidence but also by regional availability, ethnicity, drugs' safety profile, suitability during pregnancy, skin sensitivity, and the intensity of sun exposure. Topical treatments' ancillary antioxidant, anti-inflammatory, and broad-spectrum photoprotection actions should be considered.

Table 6 presents selected clinically efficacious topical agents, including new substances such as isobutylamido thiazolyl resorcinol (ITR) (Thiamidol™), niacinamide, and tranexamic acid (TA), promising alternatives with satisfactory results. However, more randomized, placebo-controlled trials involving large patient groups are needed to confirm their efficiency.[34]

Arbutin is a hydroquinone variant with a concentration-dependent melanogenesis inhibition and a component of various depigmenting products.[35]

Azelaic acid inhibits tyrosinase and has antiproliferative and cytotoxic properties against tumor cells. Its clinical efficacy is equal to 4% hydroquinone and superior to 2% hydroquinone.[36]

Glycolic acid inhibits tyrosinase, facilitates skin turnover, and reduces melanin formation. It enhances the efficacy of other topical treatments, especially on darker skin, where it works more quickly. Glycolic acid can be more irritating than hydroquinone alone, and there is a small risk of postinflammatory hyperpigmentation, particularly on dark skin. Moisturizers can help mitigate these effects.

Hydroquinone is considered as a reference for treating hyperpigmentation. It is available at 4% for the active treatment

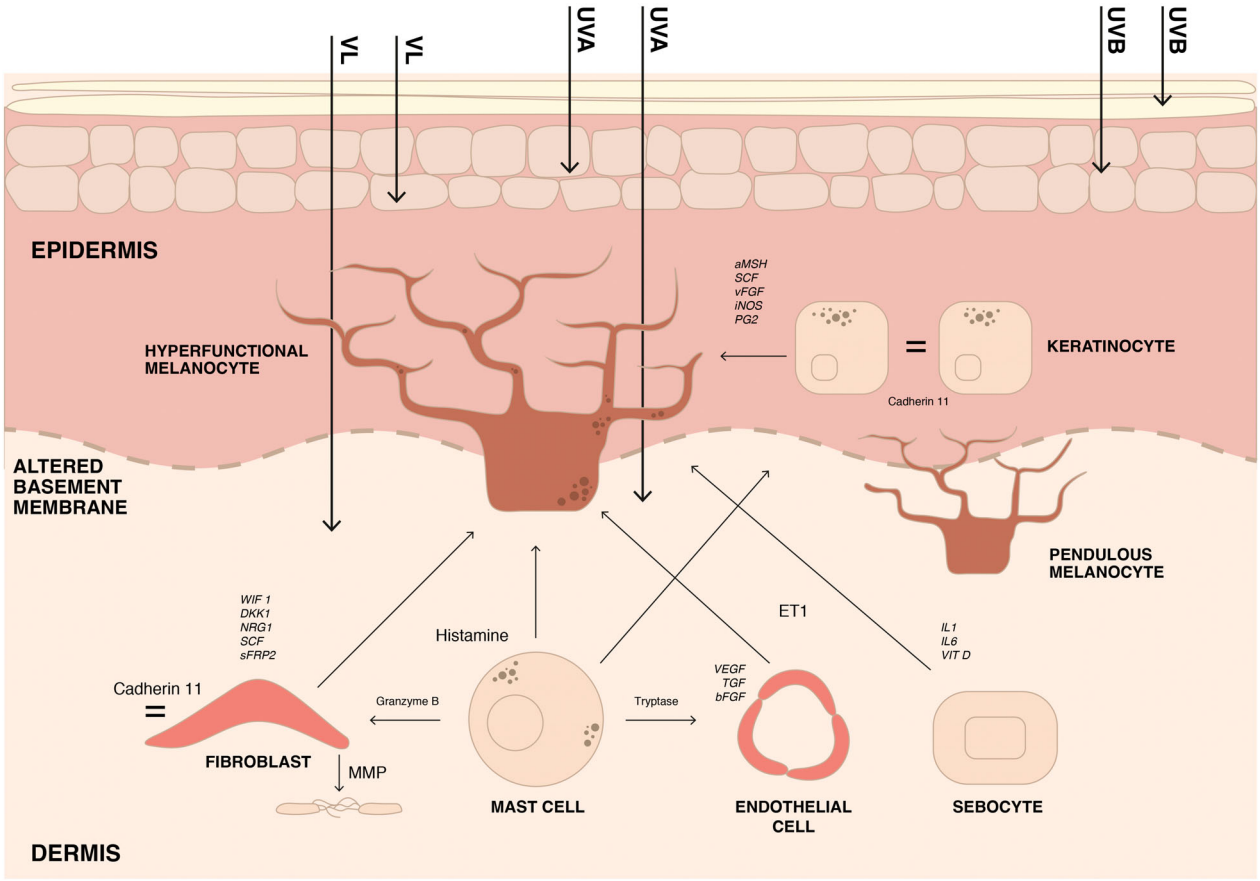

Figure 2 Different wavelengths of sun radiation, such as visible light (VL), ultraviolet A (UVA), and ultraviolet B (UVB), produce various effects on the skin's components. These radiations directly stimulate melanocytes' melanogenesis (hyperfunctional melanocyte) and indirectly through paracrine regulation. Fibroblasts' and keratinocytes' ultraviolet-mediated overexpression of cadherin 11 contributes to basement membrane damage and melanocyte migration into the dermis (pendulous melanocyte). Keratinocytes increase melanocyte proliferation and melanogenesis by secreting cytokines and hormones such as alpha-melanocyte-stimulating hormone (α-MSH), stem cell factor SCF, basic fibroblast growth factor bFGF, inducible nitric oxide synthase iNOS, and prostaglandin E2 PG2. Fibroblasts' increased expression of matrix metalloproteinases (MMP) 1 and 2 leads to collagen degradation and elastotic material accumulation in the skin. Senescent fibroblasts release several melanogenic growth factors, including Wingless-related integration site family member 1 inhibitory factor (WIF 1), Dickkopf protein 1 (DKK1), neuregulin 1 gene (NRG1), SCF, and human secreted frizzled-related protein 2 (sFRP2). Mast cells release histamine, which activates melanogenesis and tryptase production. Tryptase damages the basement membrane by degrading type IV collagen. Mast cells also induce hypervascularization by secreting vascular endothelial growth factor (VEGF), transforming growth factor (TGF), and beta fibroblast growth factor (βFGF). The inflamed endothelial cells produce endothelin 1 (ET1), which upregulates key genes for melanogenesis. Sebocytes have been suggested to influence melanogenesis by secreting cytokines such as interleukins IL1α and IL6, synthesizing vitamin D (VIT D), and producing growth factors such as angiopoietin and adipokine, which directly or indirectly modulate melanocyte function

phase and 2% for maintenance. It may cause temporary pigmentation changes, irritation, or, rarely, exogenous ochronosis. It is not recommended for pregnant or breastfeeding women or people with drug allergies.[19,37]

Isobutylamido thiazolyl resorcinol is a potent inhibitor of recombinant human tyrosinase, outperforming arbutin, kojic acid, and hydroquinone in depigmenting effectiveness. Studies have shown that ITR improves mMASI Index scores significantly better than 2% hydroquinone and is no different from 4% hydroquinone.[38,39]

Kojic acid blocks tyrosinase activity by forming chelates with copper at the enzyme's active site. It is less irritating compared to hydroquinone. In concentrations of 2%, it is a safe alternative for patients who do not tolerate hydroquinone.[40]

Niacinamide is the active form of vitamin B3 and is essential in melasma treatment. It stimulates the production of ceramides and other crucial stratum corneum lipids, strengthening the skin barrier. Niacinamide decreases pigmentation, inflammation, solar elastosis, and mast cell infiltration.[41] It improves pigmentation and decreases MASI score with no significant difference compared to hydroquinone.[36]

Tranexamic acid, traditionally used to control bleeding, is an emerging treatment for melasma. It inhibits plasminogen

Table 3 Data from studies and surveys on the epidemiology of melasma in Latin America

Country	Age group	*n*	Design	Results
Brazil[12]	18+	953	Cross-sectional, multicenter	• 97.5% women • Phototypes II (12.8%), III (36.3%), and IV (39.7%) • Higher frequency in postmenopausal women (14.2% vs. 3.5%, $P < 0.0001$)
Brazil[13]	Adults	1500	Population study	23.6% of men and 29.9% of women reported pigmentation disorders as the main cause of dermatological consultation
Brazil[14]	—	302	Semi-structured questionnaire for melasma patients in a dermatology clinic	• Intermediate skin phototypes III (34.4%) and IV (38.4%) prevailed • Mean age of onset 27.5 ± 7.8 years • Family occurrence in 56.3% • Triggered by pregnancy (36.4%), contraceptives (16.2%), and intense sun exposure (27.2%) • Zygomatic topography (83.8%), upper labial (51.3%), and frontal (49.7%)
Brazil[15]	—	686 subjects from 67 families	Complex segregation model	• 260 (38%) with facial melasma • Demonstrating an autosomal dominant inheritance genetic component
Brazil[16]	42.1 years average (SD 11.2)	515 employees	Population survey	• Melasma in 34% of women and 6% of men • Most cases are females between 20 and 35 years old
United States[20]	Latino male adults	25 poultry farmers 54 peasants 300 peasants	Direct exploration Direct exploration Teledermatology image review	Prevalence of melasma 36.0% Prevalence of melasma 7.4% Prevalence of melasma 14.0%
Peru[22]	—	1277 inhabitants of Cuzco, Peru	Direct exploration	Melasma between 4% and 10% (in a population attending a particular practice)
Brazil[16]	20–60 BC	303	Random sampling of women from the general population with facial melasma	• Prevalence 36.3% • With mMASI <4 in 72.7% • Pregnancy as a triggering factor in 49.1%

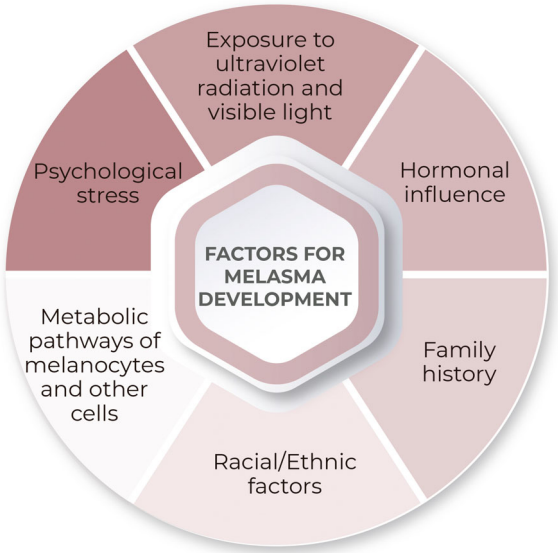

Figure 3 Most recognized factors associated with melasma

activation and limits melanocyte activity and melanin production. Compared to hydroquinone, no differences in MASI scores decrease, onset of action, and rapidity of clinical improvement are seen, and its safety profile is favorable.[42]

Triple combination cream is an FDA-approved formula containing hydroquinone, tretinoin, and fluocinolone. The combination enhances tyrosinase inhibition, promotes cell renewal, and reduces inflammation and skin irritation. However, it is not recommended for use during pregnancy or breastfeeding and may cause irritation, flaking, and burning.[38]

In addition to the topical agents reviewed above, others did not reach 75% agreement among the consensus experts for inclusion in the treatment algorithm in the first survey round and went to a second round. In the second round, 4-n-butyl resorcinol (Rucinol) and cysteamine were recommended by 67% of the participants; ascorbic acid by 44%; and pycnogenol, silymarin, and trichloroacetic acid by 33%. The reasons for this were inconclusive scientific evidence and lack of availability or limited use in the Latin American region. Retinoids and steroids alone were recommended by 56% of the participants owing to their consented use in fixed combinations.

Systemic medications

Of the systemic drugs used in melasma, oral TA has more robust evidence.[31] Its dosage varies across studies (250–1000 mg/day). Higher doses are often associated with quicker

Table 4 Statements with unanimous consensus and a ≥ 75% agreement in the Delphi surveys

- Melasma management includes the correct use of photoprotection, topical agents, systemic medications, and melasma-aimed applicable procedures.
- Adequate photoprotection is essential to prevent, treat, and avoid relapse of melasma.
- Topical agents are the prevailing component of melasma management; the decision of which agents to use is influenced not only by scientific evidence but also by regional availability, ethnicity, the drugs' safety profile, suitability during pregnancy, skin sensitivity, and the intensity of sun exposure.
- Recommended topical agents for Latin American patients are (in alphabetical order): arbutin, azelaic acid, glycolic acid, hydroquinone, isobutylamido thiazolyl resorcinol (Thiamidol™), kojic acid, niacinamide, tranexamic acid, and triple combination cream.
- Recently added topical agents, such as isobutylamido thiazolyl resorcinol, niacinamide, and tranexamic acid, are promising alternatives with satisfactory results.
- Among systemic agents, oral tranexamic acid has more robust efficacy supporting evidence, alone or combined with other treatment modalities. Other systemic agents for melasma treatment require further investigation.
- Available procedures for melasma management complement topical and oral treatments, enhancing depigmentation's speed and effectiveness when properly trained professionals use state-of-the-art techniques.
- Recommended procedures include chemical peelings, microneedling, intradermal injections, laser therapy, platelet-rich plasma (PRP), and microdermabrasion.
- Conventional and new combinations of topical agents and recommended procedures merit further exploration.
- Adding moisturizers to selected treatments helps restore the compromised barrier function in melasma-affected skin.
- Proactive relapse prevention should be incorporated early as an integral component of the treatment strategy.
- The multifactorial nature of melasma necessitates an interdisciplinary approach.
- Endocrinologists, gynecologists, and mental health professionals aware of the effects concomitant conditions in their fields have on dermal pigmentation should be consulted according to the patient's conditions.

results.[43] However, lower doses are preferred to minimize dose-dependent prothrombotic side effects. Most side effects of oral TA are transient, and it is crucial to observe formal contraindications and precautions during its use.[35] Its discontinuation may lead to relapses. Oral TA can be used either as monotherapy or combined with other treatments.[44]

Polypodium leucotomos is another systemic agent sometimes used for melasma management.[29,45] These agents may offer additional therapeutic options, although their efficacy and safety profiles require further investigation and validation in clinical settings.

Procedures

Several procedures complement topical and oral treatments to enhance the speed and effectiveness of depigmentation in melasma (Table 7).

Table 5 Identified differences between the present consensus and existing continental treatment proposals

Contributions included in the present Latin American consensus compared to similar publications for the region,[18] Mexico,[1] Chile,[28] Peru,[29] and Brazil[30]	
QoL	Although QoL was addressed, no reference was made to the convenience of professional psychological support for some patients.
Systemic factors	Hormonal, metabolic, and immune alterations associated with melasma were identified. However, none suggested referral to other specialists when these factors may play some role in disease management.
Prevention	All agree on the importance of photoprotection as a treatment pillar.
Topical agents	Classical topical agents were discussed. However, only the most recent ones mentioned new agents like Isobutylamido thiazolyl resorcinol.
Systemic treatment	Emphasis was also put on the oral use of TA, but not all mentioned other potential systemic agents.
Procedures	Laser use was the most discussed procedure. Other procedures included in the present consensus are not approached in all of them, and combination with other treatment modes is only mentioned in one.
Targeting outcomes	No prior consensus has established a specific timeline for achieving improvement to guide stepwise decision-making in management.

Chemical peelings commonly used for melasma treatment include Jessner's solution, glycolic acid (50%), tretinoin (1%–5%), salicylic acid (20%–30%), lactic acid (82%), and trichloroacetic acid (20%).[46–50] There is no clear evidence of superiority among these formulations or their sequential combination. Medium-depth peels should be avoided. Strict photoprotection is essential.

Microneedling involves creating microinjuries in the skin, promoting melanin clearance.[51] Its progressive depigmenting effect occurs over multiple sessions. It poses a lower risk of relapse compared to deeper peels.[52,53] Microneedling can be performed on individuals with darker skin tones, although the efficacy of different devices and protocols in melasma treatment is still under investigation. It also serves as a potential strategy for drug delivery by facilitating transepidermal penetration. One of the most studied applications involves using TA solution after microneedling, yielding comparable results to intradermal TA injections.[54–56]

Superficial dermabrasion has shown a low risk of melasma relapse in some studies involving hundreds of participants, but further validation is needed.[57]

Recent studies have explored the intraepidermal application of TA, which has shown promising results.[58] Intradermal injections of TA every 14–21 days have been compared with topical hydroquinone 4% and oral TA, with variable outcomes. However, intradermal TA injections do not demonstrate superiority over oral administration in treating melasma.[59]

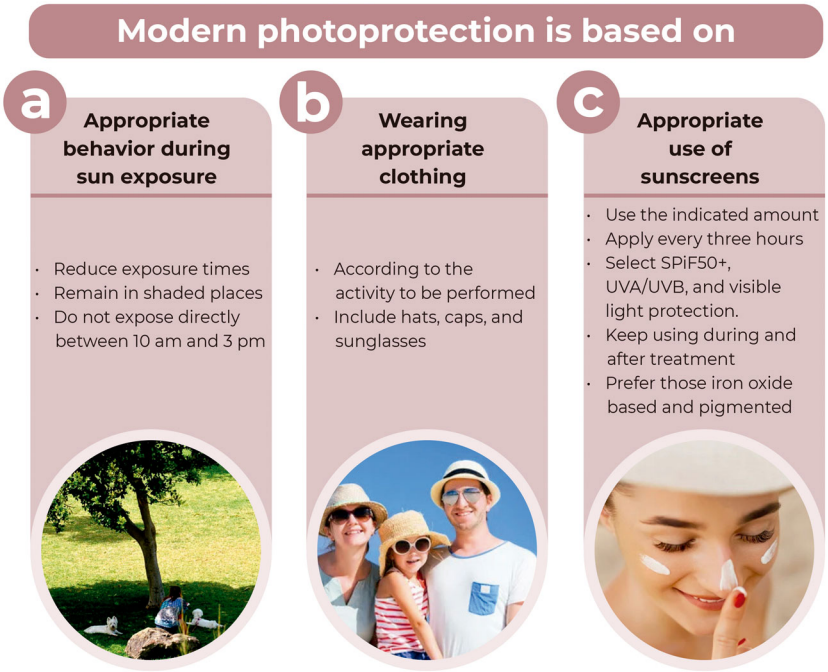

Figure 4 Consideration of all three components is crucial in primary prevention, during treatment periods, and in avoiding relapses

Injectable platelet-rich plasma (PRP) is used globally for various medical purposes. It has been studied in several controlled trials for its additional depigmentation effects in melasma, with reductions ranging from −1.1 to −4.8 mMASI points. Despite its potential, PRP remains an experimental procedure in most Latin American countries and is currently prohibited in clinical settings.[60]

Combinations

Clinical practice often combines multiple interventions to achieve faster and more effective results. Melasma treatment includes rigorous photoprotection,[61–63] topical melanogenesis inhibitors, and various adjuvant therapies such as laser/light treatments, intralesional therapy, antioxidants, and oral TA.[31]

The triple combination of hydroquinone, tretinoin, and a fluorinated corticosteroid has demonstrated superior efficacy in treating melasma compared to individual agents alone.[64–66]

Several combinations of active ingredients, such as ITR, retinoic acid, and dexamethasone, have shown efficacy in improving melasma.[67] Further exploration of nonphenolic actives in combination therapies is warranted to mitigate melanocyte toxicity.

New clinical interventions undergo rigorous testing against established treatments (e.g., triple combination or 4% hydroquinone) to develop robust evidence of efficacy in the melasma treatment.[68,69]

Owing to the compromised barrier function observed in melasma-affected skin, it is advisable to combine treatments with moisturizers. Combining hyaluronic acid with ITR has been shown to enhance clinical outcomes.[39,70]

Combining oral TA with microneedling has optimized melasma improvement, achieving a clinical reduction of 50% in 60 days compared to 30% with the triple combination alone.[54]

Laser or light therapies are typically combined with strict photoprotection and topical melanogenesis inhibitors, contributing to accelerated results in melasma treatment.[71,72]

Algorithm for the treatment of melasma in Latin America

The expert group of the Latin American consensus on the Treatment of Melasma proposed a management algorithm (Figure 5) to personalize the management of melasma according to the individual circumstances of each patient and the treatment setting. The specific details and usage of the therapeutic options mentioned in the algorithm can be found in the preceding sections.

Following the initial evaluation of melasma, and based on its severity, patients are categorized into two groups: mild (mMASI ≤5) or moderate to severe (mMASI >5). For both groups, it is recommended to start with sun photoprotection measures and concomitant administration of a topical depigmenting agent such as (in alphabetical order) arbutin, azelaic acid, glycolic acid, hydroquinone, ITR, kojic acid, niacinamide, TA, triple combination cream. These agents can be used alone or in combination according to their properties and safety profiles. In the moderate to severe group, oral TA or other systemic medication is added, combined with available technological procedures as needed. Evaluation of efficacy in melasma clinical trials ranges from 8 to

Table 6 Presiding characteristics of topical agents used for the treatment of melasma in Latin America

Active ingredient	Mechanism of action	Application method[a]	Side effects
Arbutin	Tyrosinase reduction and melanocytes' maturation inhibition. Low toxicity	Twice daily	Allergic contact dermatitis
Azelaic acid	Tyrosinase inhibition	Once in the evening	Irritation
Glycolic acid	Tyrosinase inhibition	Depends on concentration (two to three times per week)	Irritant contact dermatitis
Hydroquinone	Tyrosinase, peroxidase, and melanocyte inhibition. Melanocyte cells' membrane destruction	Once in the evening for up to 6 weeks	Irritation Hyperpigmentation (Ochronosis) Allergic contact dermatitis
Isobutylamido thiazolyl resorcinol (Thiamidol™)	Human tyrosinase inhibition	Two to four times a day	Irritation
Kojic acid	Tyrosinase inhibition	It depends on the concentration	Irritant contact dermatitis
Niacinamide	Melanosome transfer and melanocyte inhibition. Solar elastosis reduction. Anti-inflammatory and antiaging effect (via ceramide production stimulation). PAR-2 inhibition	Once daily, combination recommended	Irritation
Tranexamic acid	Tyrosinase and melanocyte inhibition. Mast cells' negative regulation. Plasmin inhibition (via arachidonic acid and α-MSH reduction). Solar elastosis, VEGF, and Endothelin 1 reduction	Twice daily	Irritation
Triple combination cream	Tyrosinase, peroxidase, and melanocyte inhibition. Melanocytes' membrane destruction. UVB-stimulated keratinocytes and tyrosinase transcription inhibition. Melanosome transfer reduction. Keratinocyte turnover increase. Mast cell recruitment and maturation Inhibition. Anti-inflammatory effect	Once in the evening for up to 6 weeks	Not recommended in pregnancy and breastfeeding Irritation

Listed agents were selected for their clinical efficacy and widespread availability in Latin America. They appear in alphabetical order.
α-MSH, alpha-melanocyte-stimulating hormone; PAR-2, protease-activated receptor 2; VEGF, vascular endothelial growth factor.
[a]The suggested application method is for topical use and may vary according to patients' characteristics, tolerability, other topical agents' concomitant use, systemic medications, or accompanying procedures.

12 weeks.[40,73–75] In clinical practice, an efficacy review should be performed after 6–8 weeks of treatment initiation in both groups, as agreed by 78% of the participating experts (the other 22% noted it might be extended up to 12 weeks at the treating physician's discretion). If an improvement of 30% or more in the mMASI is detected, it is recommended to maintain the established treatment until the maximum effect is reached. Subsequently, move to the maintenance phase where photoprotection is preserved, systemic drugs and procedures (if applicable) are discontinued, and a topical depigmenting agent is continued (reducing the frequency of application of phenolic derivatives such as hydroquinone or triple cream). Preference should be given to permanently applied cosmeceuticals with no long-term adverse effects.

If the mMASI improvement in patients with mild melasma after 6–8 weeks of treatment was less than 30%, consider adding oral medication and proper procedures.

If improvement after 6–8 weeks of treatment was less than 30% in patients with moderate to severe melasma, adjust depigmenting agents, systemic medication, and interdisciplinary procedures; reassess at 6–8 weeks.

If melasma relapses at any time or resistance to treatment appears, reevaluate the case as a new scenario and restart with the algorithm's initial flow.

Keep in mind consultations with other specialists to rule out associated pathologies.

Prevention and relapse management

No treatment is entirely curative for melasma as yet, and relapses are common, even after a positive response to treatment. Therefore, proactive relapse prevention should be incorporated early as an integral component of the treatment strategy.

Certain factors have been identified as contributing to an increased likelihood of relapse, such as the discontinuation of oral TA and triple combination therapy. Ablative and proinflammatory treatments, including medium peels and rejuvenation procedures, as well as sun exposure, noncompliance with maintenance treatment, lack of protection against broad-spectrum solar radiation, hormonal therapy, and pregnancy, are associated with an increased risk of relapse. In contrast, interventions such as microneedling and gentle microdermabrasion have been reported to result in lower relapse rates.[33,52,54,76–79]

Table 7 Relevant procedures for the treatment of melasma

Chemical peelings
• Classical adjuncts in the treatment of melasma
• Enhance epidermal turnover, resulting in the clearance of melanosomes
• Cost-effective, with minimal downtime, and can improve treatment results
Microneedling
• Leads melanin clearance through multiple superficial perforations from the epidermis to the upper dermis, promoting neocollagenesis, fibroblast replication, and a high rate of epidermal turnover
• Tranexamic acid can be used by this route
• Can be conducted using robotic devices or needled rollers
• Sessions can be performed every 14 to 28 days, and there is minimal downtime
Laser therapy
• Short-pulse (nanoseconds) lasers destroy melanin by photoacoustic effects, such as Q-switched and ultrashort-pulse (pico-seconds) lasers
• Picosecond lasers have the least inflammatory and photothermal effects
Microdermabrasion
• Reported as an effective adjuvant treatment, resulting in a low risk of relapse
• Subsequent trials are needed to validate this procedure
Intradermal injections
• Several solutions, such as tranexamic acid, vitamin C, glutathione, triamcinolone, and hyaluronic acid, have been studied
• Systematic investigations are still pending
Platelet-rich plasma injection
• Relies on the release of growth factors from intradermally injected, highly concentrated platelets
• Exhibits significant variability in terms of activation, centrifugation regimens, final platelet concentration, and treatment protocols
• Variations pose challenges to the consistency and reliability of results across different studies

Procedures that may complement topical and oral treatments to intensify depigmentation's speed and effectiveness.

It is crucial to differentiate relapse from resistance or treatment failure, where the condition does not show improvement despite treatment efforts.

Multidisciplinary approach

The multifactorial nature of melasma necessitates an interdisciplinary approach. Although current evidence is insufficient for specific recommendations, there is consensus on the importance of involving endocrinologists, gynecologists, and mental health professionals when the patient's condition warrants it. These specialists should be aware of the effects of common conditions in their fields on dermal pigmentation.

Thyroid hormones, among other endocrine factors, have been linked to the development of melasma.[80] A meta-analysis observed that serum levels of thyroid-stimulating hormone and thyroid peroxidase antibodies were higher in patients with melasma, particularly in women.[81] Other authors have corroborated these findings.[82,83]

Melasma most often occurs in women of childbearing age and those who use oral contraceptives.[80,84,85] In this group, changes such as increased transcription of tyrosinase and dopachrome tautomerase, which enhance physiological pigmentation, are intensified by ovarian and placental hormones that promote pituitary hormones.

The relationship between melasma and hormonal alterations in men remains controversial. Some studies report hormonal alterations in only 9.7% of male patients with melasma, while others have detected decreased testosterone levels.[23,86,87] Additionally, some reports link the increase in melasma to the widespread use of finasteride[88] and the administration of exogenous estrogens to men.[89]

Several skin conditions, including melasma, significantly impact patients' mental health and psychological well-being. When detected, emotional and psychological support, including professional psychological intervention, is essential.[90,91]

It is advisable to consider a thyroid profile, a female or male hormonal profile as appropriate, and psychological assessments of mental, mood, or psychiatric status. Additional evaluations, such as tests for metabolic syndrome or liver function, may be required based on availability and the specific needs of each case.

Perspectives on the treatment of melasma

Over the years, understanding melasma's pathophysiology and treatment has evolved into a sophisticated multimodal approach. With growing knowledge of melasma's pathogenesis, new and effective treatments are being incorporated into the therapeutic arsenal, such as VL protectants containing iron oxide, novel topical agents like pigment-correcting serums and flutamide, and oral administration of *P. leucotomos*.[92]

Current melasma treatments incorporate new agents that target various aspects of the condition, from classic approaches attacking the melanogenesis pathway to novel strategies addressing overactive melanocytes, reducing inflammation and free radical production, and inhibiting melanosomal transfer to keratinocytes, among other pathways.[93]

Advanced imaging techniques such as reflectance spectroscopy and reflectance confocal microscopy are gaining traction for diagnosis. These techniques provide detailed analyses of melasma characteristics at the cellular and molecular levels. These advancements open new possibilities for personalized treatment, marking a more sophisticated melasma evaluation and management era.

Procedures complement underlying treatments. Microneedling, for example, can enhance their effectiveness and delay relapses. Phenol-croton peels show promising results in long-term remission. Other technologies, such as TA intradermal therapy, PRP, and various laser techniques (e.g., picosecond pulse laser and pulsed dye laser), are also being explored.[31]

The accumulation of advanced glycation end products (AGEs) contributes to the yellowing of photoaged skin and may

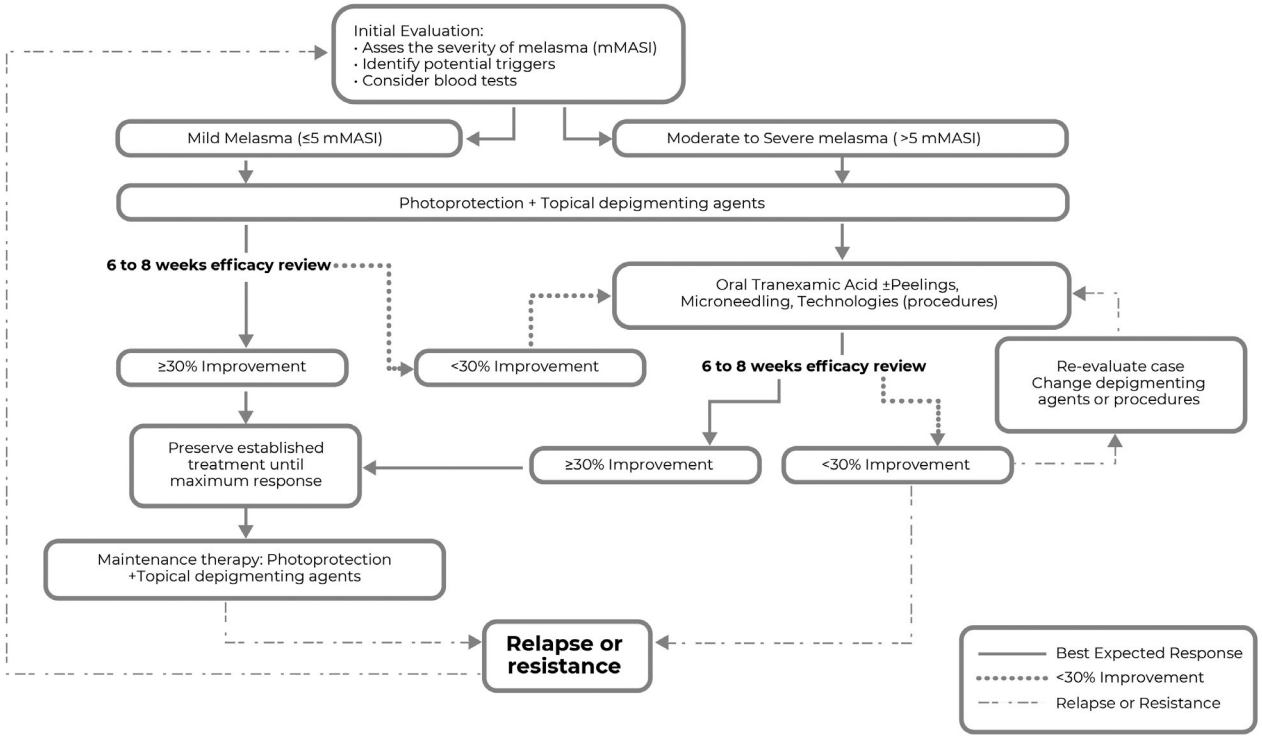

Figure 5 Best expected response—after an initial evaluation, photoprotection, and topical depigmenting agents should be started for mild and moderate to severe melasma patients. In the moderate to severe group, start oral tranexamic acid and add treatment procedures as needed. Review efficacy after 6–8 weeks of treatment. With a > 30% mMASI improvement, continue the established treatment until the maximum response, followed by maintenance therapy. <30% mMASI improvement (at the 6–8 weeks efficacy review)—For the mild group, start oral tranexamic acid and add treatment procedures as needed. For the moderate to severe group, reevaluate the case and adjust the depigmenting agent, oral therapy, or procedures as required before the following 6–8 weeks efficacy review. Relapse or resistance—This can occur at any time during treatment. Restart with the algorithm's initial flow

play a role in hyperpigmentation disorders. Increased levels of AGEs have been observed in the dermis of sun-exposed skin, melasma, and lentigo solar lesions, suggesting a potential direct promotion of epidermal melanin levels.[94,95] Various natural compounds are being investigated for their potential to inhibit AGE formation, with ongoing studies to define their mechanisms of action, safety, and efficacy.[96]

Photobiomodulation is emerging as a promising, noninvasive procedure for melasma treatment. This technique uses lasers or other low-intensity light sources to achieve therapeutic effects without causing destruction. The most used spectral regions are red (600–700 nm) and near-infrared (780–1100 nm). Photobiomodulation can potentially reduce erythema and vascularization, improve dermal conditions,[97] and possibly help develop future resistance to UV rays.[98]

The skin microbiome plays an important role in various skin disorders and is a significant immune system regulator. Probiotics have been shown to have distinct advantages in skin disorders, including melasma, because of their anti-inflammatory activities, antioxidant properties, UV protection, and tyrosinase inhibition activity. Certain strains of gut microbiota, such as *Collinsella* spp., may influence the appearance and development of melasma.[99] Promising probiotics that inhibit melanin production and tyrosinase activity, leading to skin lightening, include *Bifidobacterium adolescentis*, *Lactobacillus helveticus NS8*, and *Rhodobacter sphaeroides*.[100]

Today, melasma is considered a dynamic process, with new treatment strategies emerging from a better understanding of its pathogenesis. Ongoing clinical trials are helping identify triggers and refine therapeutic approaches.

In conclusion, managing melasma as a chronic, relapsing condition presents challenges, particularly given the diverse populations across Latin America. Successful interventions must consider individual characteristics such as skin tone, triggering factors, disease severity, prior treatment experiences, pregnancy status, and sun exposure habits.

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