Australasian Society of Cosmetic Dermatologists

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VOLUME 01 / ISSUE 01 / DECEMBER 2020

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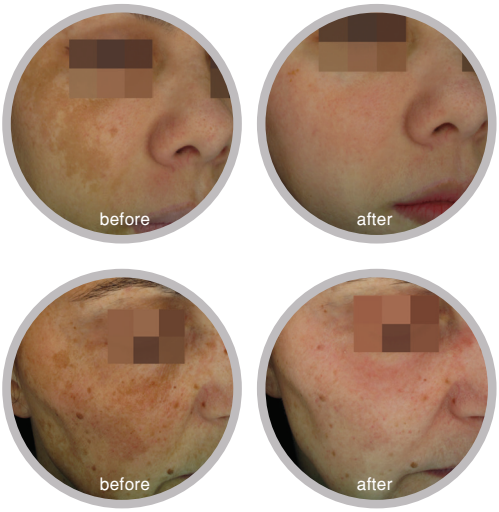

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OPINIONS AND PROGRESS IN
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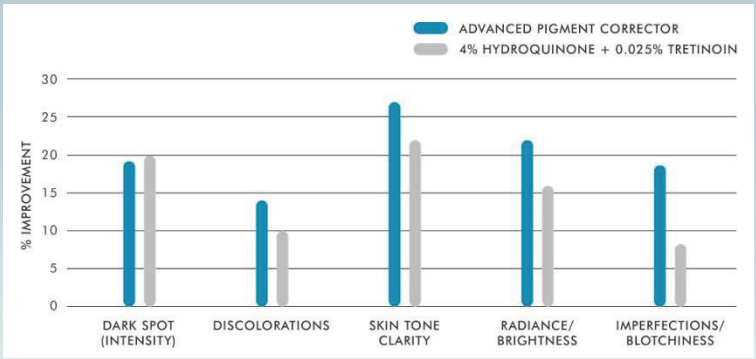

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OPINIONS AND PROGRESS IN
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Welcome to the inaugural edition of **Opinions and Progress in Cosmetic Dermatology**

It has been an incredibly challenging year for all of us with COVID-19 causing significant disruption to all aspects of our usual day-to-day life. It has meant that we have all lived through various restrictions affecting how we as healthcare professionals deliver care as well as access continuing professional development. Whilst we had been planning to launch this journal with the Australasian Society of Cosmetic Dermatologists (ASCD) this year, we never envisioned the extra education needs that arose from COVID-19, which grounded planes and forced education online.

Opinions and Progress in Cosmetic Dermatology plans to be a themed quarterly journal to allow scientific exchange as well as interaction with industry to ensure the best clinical outcomes for our patients. It is the official journal of the Australasian Society of Cosmetic Dermatologists and will feature peer-reviewed scientific articles, review articles, selected case studies as well as academic key opinion pieces. The format of the journal aims to be innovative but practical, with lots of helpful tips and tricks of the trade.

Hopefully the world will find its way and we will be able to meet face-to-face again soon at the next ASCD event. In the meantime, we are excited to bring to you this first edition and look forward to it being the 'must read' to help keep you up to date.

Co-Editors in Chief
Dr Adrian Lim
Assoc Prof Saxon D Smith

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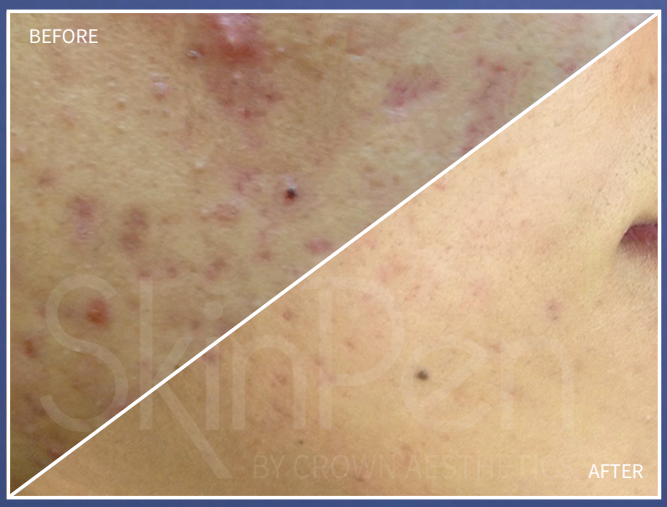

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“Best of Melasma”

Guest Editor: Dr Sachin Vaidya[1, 2]
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Disclosures: *none*

Vaidya S. Best of Melasma. Opin Prog Cosmet Dermatol 2020;1(1):1.

This is the first edition of the journal of the Australian Society of Cosmetic Dermatologists (ASCD). It is a compilation of up to date literature on the topic of melasma. This edition includes historical aspects of melasma, evolving and complex pathophysiology with potential treatment targets, and advances in diagnosis. It also covers the current best medical management of melasma. The various energy-based devices that have shown success in recalcitrant cases are discussed.

Melasma is a common condition seen in skin of colour. It is a difficult condition to treat considering its high relapse rate. It has a significant impact on the quality of life of patients, causing emotional, psychological, and social stress.[1]

Recently the role of visible light has been recognised and sun protection with particular emphasis on protection from visible light has become an essential part of management. The shorter wavelengths (blue violet) of visible light act on melanocytes through the activation of opsin 3 (OPN3), a sensor for visible light pigmentation.[2]

Topical bleaching agents and strict sun protection remain the mainstay of treatment. Oral tranexamic acid has shown success with minimal reported complications.[3,4] It has become a game changer in the management of melasma. In recent years, use of topical and intradermal injections of tranexamic acid has been reported in refractory melasma cases.[5] Radiofrequency and laser-assisted delivery of various agents has been tried in last few years.[6,7] Qs Nd:YAG, picosecond, 1927 nm thulium laser and other energy-based devices are currently third line treatment options, however in the future, these may prove to be more effective.

Overall, this edition is a representation of the current understanding of new management modalities for melasma and introduces what is on the horizon.

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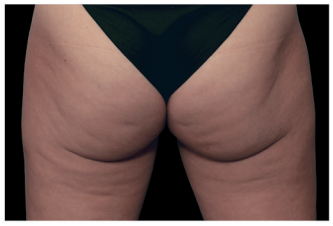

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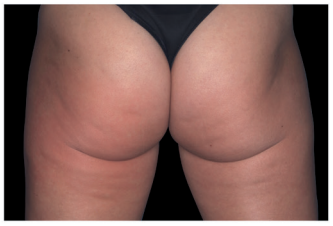

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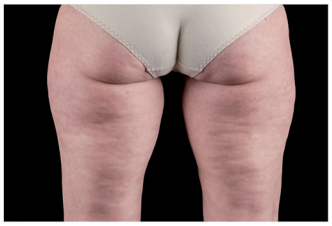

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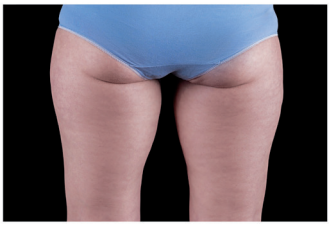

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History of Melasma

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KEY WORDS: melasma; hypermelanosis; skin; historical; perspective

Saxon SD. History of Melasma. Opin Prog Cosmet Dermatol 2020;1(1):4.

Melasma is a chronic acquired dysfunction of melanogenesis that results in localised hypermelanosis of the skin. It typically occurs symmetrically on sun exposed areas of the body particularly on the face, and is more common in women in menache.[1]

However, melasma is not a new condition. In fact, the word melasma has its origins in the Greek root "melas", which means black. This refers to its brown pigmentation that is classic of the clinical presentation. Not only does melasma owe its origins to a Greek derivation of the name, but also the first disease descriptions date as far back as Hippocrates (470-360 BC).[2] At this time, there was a recognition of the association of developing pigmented spots during pregnancy, and with general diseases such as inflammatory dermatoses. There was also the start of an awareness of a relationship between exposure to sunlight and increased pigmentation of the skin.

Melasma resurfaced many years later as a specific medical condition in the published works of Joseph Plenck (1735-1807AD). Joseph Plenck was an Austrian physician and a pioneer in dermatology.[3] In 1776 he published a classification of skin diseases entitled *Doctrine of Morbis cutaneis*.[4] It was in this book that he proposed seven variants of 'melasma' which he termed *'ephelis'*: *solaris*; *ignealis*; *vesticario*; *gravidarum*; *hepatica*; *dismenorrhoealis*; *and*, *haemorrhoidalis*.

In modern Western medical literature, a 1934 paper described the case of an unmarried 20 year-old woman from London, England, with a 2 year history of pigmentation affecting the upper lip with well-defined margins and a varying intensity which was worse with sun exposure.[5] In 1961, a case series of 15 patients from Los Angeles, USA, between the ages of 25 and 43 years, presented with symmetrical dyschromia of the face of unknown aetiology.[6] The dyschromia was characterised by the "insidious development of a blotchy hyperpigmentation of the face". They describe that the adult women (n=14) were essentially healthy. However, this appears to be the first time that a man (n=1) had been reported to have melasma.

Fast forward to 2020 and melasma is recognised as a common condition which remains challenging to treat in many circumstances.

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A Summary of OPCD Proceedings: Melasma

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Disclosures: *none*

Goodman GJ. A Summary of OPCD Proceedings: Melasma. Opin Prog Cosmet Dermatol 2020;1(1):5-9.

Our new journal is underway thanks to the stewardship of Co-editors in Chief, Drs Saxon Smith and Adrian Lim. As their introduction discusses, we are an open access quarterly online themed journal appropriate in a time of pandemic and into the future.

My role is to roughly summarise this issue highlighting points that are memorable and important in this our first issue, discussing melasma.

Introduction

We are indebted to Dr Sachin Vaidya, our first guest theme editor, featuring that most intriguing and difficult disease complex – melasma. His editorial emphasizes the following points:

- Melasma has significant impact on the quality of life of patients.
- Visible light may also impact on melasma through activation of Opsin 3(OPN3), a sensor for visible light pigmentation.
- Topical bleaching agents and sunscreens remain the mainstay of treatment.
- Oral tranexamic acid (TA) appears a very useful adjunct with few complications with appropriate patient selection. Intradermal and topical TA with and without fractional assisted delivery are being explored as non-systemic alternatives.
- Third line are Q-Switched and Pico lasers, 1927nm Thulium and other energy-based devices.

History

Dr Saxon Smith then examines the history of melasma:

- That the term melasma has its origin in the Greek root “melas” that means black, dating back to the days of Hippocrates.
- An Austrian physician Joseph Plenk in 1776 published and classified melasma into seven variants.
- More recently in 1930’s Corsi described a single case but it took till 1961 for a case series to be reported leading to the beginnings of the current rich literature but it still remains a challenging condition.

Pathogenesis

Drs Tran, Nguyen and Vaidya next discuss the pathogenesis of melasma:

- Melasma remains a multifactorial disease.
- Genetics playas a part with a family history in many cases and a higher prevalence in darker skin types. Downregulation of inhibitory genes in melanin production and upregulation of tyrosinase encoding genes with consequent increase in melanocyte stimulating factors and proteins may vary between individuals.
- Sun exposure via both ultraviolet and visible light (especially blue-violet light) activates melanocytic behaviour. This occurs both directly and indirectly.
- Hormones have shown through pregnancy, OCP and HRT effects with both oestrogen and progesterone being implicated by receptor activation and enzyme induction.

- Vascular factors seem to be one of the more recent and fascinating pathogenic factors with UVL stimulation of vascular endothelial growth factor (VSGF) being one interplay between the vascular and melanocytic pathways.

- The Basement Membrane seems to have some involvement with leakage of this barrier being responsible for dermal melanin in melanophages.

- Solar elastosis seems over expressed in melasma zones and possibly histamine which is prominent in elastotic areas may stimulate melanin production.

- Sebaceous gland territories seem to correlate with melasma distribution and through sebocyte synthesis of vitamin D, cytokines and growth factors may affect melanocyte function.

- Reduced expression of microRNAs, nucleotides expressing non-coding RNA may have a role in melanogenesis and melanosome transfer.

Diagnosis and diagnostic tools

In two articles touching on diagnosis Dr Davin Lim and Drs Gupta, Doolan and Manungo take us through the diagnostic tools for establishing the diagnosis of melasma:

- Both explain that the diagnosis of melasma relies much on its typical pattern of lateral cheeks, sparing of the periocular area and upper lip involvement. Gupta, Doolan and Manungo emphasise the forehead and extrafacial involvement of forearms in sun exposed zones and the reddened or inflamed facial variants of melasma (erythrosis pigmentosa faciei). Lim and Jibreal discuss the subtlety of clinical diagnosis as shown by the jawline melasma variant that may be difficult to separate from Poikiloderma, or by post inflammatory pigmentation that may require history to differentiate from melasma.

- Both manuscripts discuss the role of the simple Wood's light (UV emitting lamp 320-400nm) in helping to determine the depth of pigment: enhanced with epidermal, grey macules or pigment disappearance with dermal and spotty enhancement when mixed. Gupta, Doolan and Manungo point out limitations of sunscreen use, darker skin phototypes and that its typical interpretation may be not as accurate when compared with histopathology.

- Dermatoscopy is felt to be important by both sets of authors. Lim and Jibreal use it in differentiating freckling (uniform pigment with a moth-eaten edge), Hori's naevus (grey, structureless and devoid of telangiectasia) and lentigines (scalloped borders moth eaten appearance) from melasma. Gupta, Doolan and Manungo discuss the typical melasma findings – epidermal with "patchy or homogenous reticular pigment network with light to dark brown globules and granules with perifollicular sparing", Dermal melasma "is more heterogenous with greyish brown or greyish blue-black irregular pigment network that is less responsive to treatment", The amount of vascularity may be well assessed by dermatoscopy and may help direct management.

- Gupta, Doolan and Manungo discuss the role of histopathology and confocal microscopy. Histopathology may show solar elastosis consistent with photodamage photodamage, basement membrane disruption with melanin dermal dropout and melanophage activity, telangiectases, increased mast cells but no difference in numbers of melanocytes.

- Confocal microscopy acts as a non-invasive histology tool, allowing delineation of where the pigment is residing but remains a research tool at this time.

Management

Dr Davin Lim discusses his "pearls" in melasma management and provide a treatment pyramid from "ground zero" to 4th tier:

- First should come sun protection and education.

- Next in line are the pigment correcting agents both Hydroquinone and combination products and other agents including botanical bleaching agents (Ascorbic acid, azelaic acid, arbutin, hydroxy acids, Kojic acid) and novel agents such as cysteamine.

- Emerging and established therapies include oral tranexamic acid represents the next tier.

- Physical therapies including microneedling with or without transepidermal delivery, superficial peels, lasers (low fluence Q-Switch YAG, Pico and Thulium fractionated lasers may be necessary in cases but are usually best placed as last resort treatments.

- All therapies have issues with rebound, secondary rashes such as irritation, tachyphylaxis, contact dermatitis, post-inflammatory hyperpigmentation, ochronosis and from tranexamic acid – possible increased thrombotic issues in susceptible individuals.

In addition, So and Riodrigues discuss the role of:

- The modified MASI score (mMASI) in quantitating melasma severity.
- Counselling the patient on the chronicity and recalcitrance of the disease.
- Modifying lifestyle, relying on shading the skin and wearing make-up and foundations.
- Topical bleaching agents either alone or in combination highlighting retinoids, azelaic acid and vitamins and, like Lim and Jibreal, highlight newer agents like 15-minute application of 5% cysteamine.
- Oral therapy with tranexamic acid is also highlighted but with the warning that this should be avoided in Covid 19 at risk populations due to the pro thrombotic effects of the coronavirus.

Cosmeceuticals

Dr Zoe Draelos discusses cosmeceutical agents in melasma therapy. Amongst her main take home messages are:

- Sunscreens need help in controlling melasma.
- Hydroquinone is still the mainstay of treatment but its melanotoxicity could limit its use into the future as may be the fate of its most similar agent in kojic acid. Often these agents are used with other added agents to enhance activity by targeting other aspects of melanocyte behaviour.
- Naturally occurring agents such as liquorice extracts which are glycosides containing flavonoids are commonly used.
- Aloe vera derived Aleosin, sometimes combined with Arbutin a naturally occurring gluconopyranoside both target tyrosinase.
- Vitamin C interrupts melanin synthesis by interacting with copper ions to reduce dopaquinone and blocking dihydroquinol-1-2-carboxyl acid oxidation.
- Combining agents is the best option in most patients.

Devices

In the article on the use of devices in melasma by Drs Gold, Levy, Utley and Lee there were some salient points raised:

- There is no miracle cure for melasma.
- Intense pulsed lights may be successful with quite a number of studies illustrating their benefit on reducing MASI scores even in darker phenotypic patients.
- Q Switched lasers may also work but need to be set at low fluence and require multiple treatments. Picosecond lasers seem to be more effective, with less incidence of post inflammatory pigmentation and fewer treatments.
- Fractional non-ablative lasers with various wavelengths (e.g. 1440, 1550nm) have good outcomes with MASI reduction but the incidence of PIH was significant. Thulium laser (1927nm) may have a better outcome and a combination of 1550 and 1927nm is useful.
- Vascular lasers such as pulsed dye lasers may be useful as there appears to be a vascular component in many cases of melasma.
- Whatever device is used it would appear that maintenance is important.

Debate

The next two articles are the beginnings of a regular feature of OPCD journal issues and offers opinion pieces arguing from different viewpoints.

In the first of our debate topics, and in a spirited defence of the primacy of place of topical therapy in the treatment of melasma, Dr Shawn Richards purports that:

- Melasma should be thought of as any chronic disease and that control is the aim.
- A 2010 Cochrane and more recent reviews all favour topical therapy when efficacy and safety are considered over chemical peels and lasers and other energy-based devices.
- One needs to be sceptical of claims of the newest device that may be touted as the panacea for this disease.

- Devices tend to show initially good results but are compounded by paradoxical pigment issues with PIH and confetti hypopigmentation complicating these treatments.
- Devices may render initially speedier results, but topical therapy comes into its own in the longer term.
- Oral tranexamic acid has emerged as a very useful second line therapy possibly positioning devices to end-of-line treatment.

In counterpoint to a mainly topical approach Drs Manoharan and Seine make the case for an all-inclusive approach to maximise patient outcomes and satisfaction. He emphasises that:

- Topical therapy does not always work.
- Physical treatments in chronic conditions such as psoriasis are considered part of standard therapeutics, so why not in the equally chronic melasma cases.
- Treatment needs to be individualised.
- Oral therapeutics such as tranexamic acid and glutathione (e.g. a 500mg buccal lozenge) are gaining traction.
- Chemical peels will help especially in superficial melasma by desquamation of epidermal laden pigment and should not be discounted with lactic acid the best studied.
- Many energy-based devices have been studied, albeit in small series but appear to have a significant role. However, devices need the back up of topical and even systemic therapy to limit the risk of PIH.
- All devices elaborated in other articles in this journal such as QSL, fractionated ablative and non-ablative devices, IPL, Pico lasers and PDL all have literature to show efficacy. However, many of these technologies need skilled practitioners to allow a satisfactory safety profile to therapy.
- A combination approach may allow more rapid clearing and a plan for patients may need to include energy-based devices in some.

Complications

In a provocative review of possible complications Alvin Lim and Davin Lim discuss the issues centering around the chronicity of the disease and the search for consequent long-term therapy without significant adverse reactions.

- Sunscreens are not without issues with contact and irritant dermatitis especially fragrances and preservatives but also UV filters such as benzophenones and dibenzoylmethanes, carcinogenic and endocrine effects (oxybenzone), photodegradation and photosensitivity (Avobenone and derivatives).
- Hydroquinone with or without combination with other agents may induce irritation, erythema, milia, PIH and transient and permanent hypochromia, the black grey hyperpigmentation such as ochronosis.
- Other hypopigmentation agents such as azelaic acid, adapalene and other retinoids, kojic acid all share irritation, burning and erythema as adverse reactions. Cysteamine and vitamin C may be good alternatives.
- Natural ingredients such as liquorice, orchid, green tea, turmeric, arbutin, coffeeberry, and mulberry extracts seem to have less documented adverse reactions.
- Oral tranexamic acid appears to have an adequate efficacy and safety profile but may cause gastrointestinal adverse reactions, oligomenorrhoea, headache, myalgia, palpitations, urticarial rash with angioedema, and neurological effects. The thromboembolic effects need to be borne in mind and careful patient selection employed.
- Intense pulsed light may only be suitable for fairer skin types with melasma with erythema, burning, stinging, erythema and recurrence being common post therapy. These adverse effects are shared to some degree with lases such as non-ablative and ablative fractional resurfacing and pulse dye lasers. Q switched 1064nm lasers have the additional issue of long-term mottled hypopigmentation when used frequently (low fluence and at least two weeks between treatments) and picosecond lasers need more time to assess their long-term effects.
- Peels (TCA, glycolic, salicylic acid, mandelic acid, lactic acid, tretinoin) are variably useful but are all prone to occasional erythema and resultant PIH with salicylic acid and mandelic acid being the better choices for darker skin types.

The Future

Drs Rashmi Sarkar and Preethi Nayak have given us a glimpse into the future and whether this offers some increased hope for patients suffering from melasma. They have divided this up along the lines of pathogenic mechanisms. They suggest:

- Looking at hyperactive melanocytes by antioxidant substances such as flavonoids, liquorice extracts, ascorbic acid, aleosin and hydroquinone simulants targeting the enzymes (tyrosinase) and genes controlling hyperactivity (TYRP1, TYRP2 and MITF).
- Looking at melanosome transfer inhibition through inhibiting keratinocyte protease activated receptor 2 (PAR2). Agents such as niacinamide, liquirtin, soy, lectins may have a role.
- Reducing oxidative stress – virtually all antioxidants may have a role here with vitamins, A,B, E,C, Glutathione, pycnogenol and melatonin amongst others being useful here.
- Vascular components such tranexamic acid may be the forerunner to further targeting of vascularity.
- Oestrogens upregulate enzymes responsible for melanin synthesis such as tyrosinase, TRP1,2 and MITF. Maybe into the future triple therapy may be a hydroquinone, and anti-oestrogen and a Vascular Endothelial Growth Factor.
- Histamine and mast cells are increased in areas of melasma and may be targets for therapy. Oral tranexamic acid and zinc may target mast cells.
- Amongst others, curcumin, lignin peroxidase and platelet rich plasma and drug delivery by micro needling may hold promise.

We are obviously excited about our first issue coming to fruition. It offers us a huge advantage of opinion, personal recommendation, evidence-based reasoning from experienced opinion leaders. We hope it will offer you a valuable reference on this vexing topic. It will always be openly available to our ASCD community. We believe in openness of science and the value of its sharing and comment.

Our next Journal Issue

Our next topic is no less contentious and difficult. Rosacea is protean in its presentation, variable in response to treatment, incompletely understood and hated by patients. Dr Belinda Welsh is our guest editor for this issue and we look forward to presenting this to all of you in the end of the first quarter of 2021.

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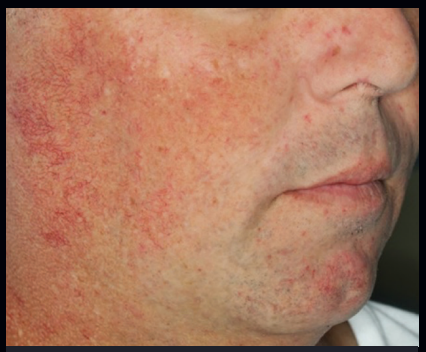

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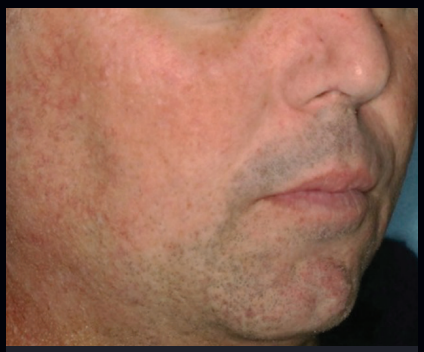

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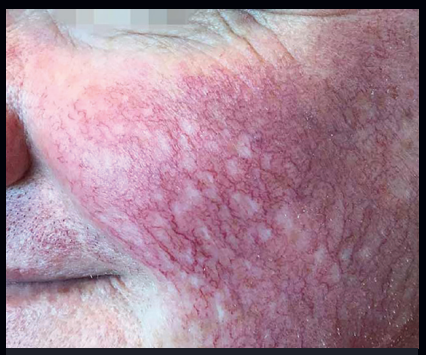

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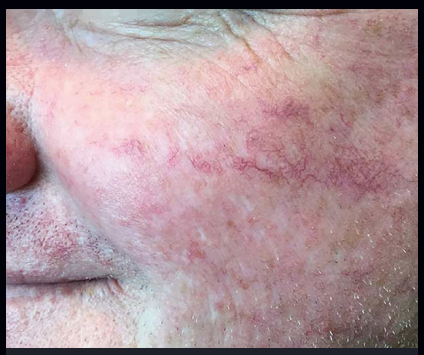

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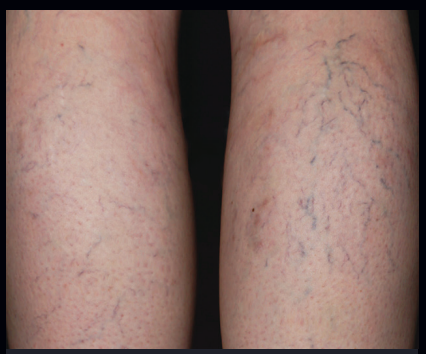

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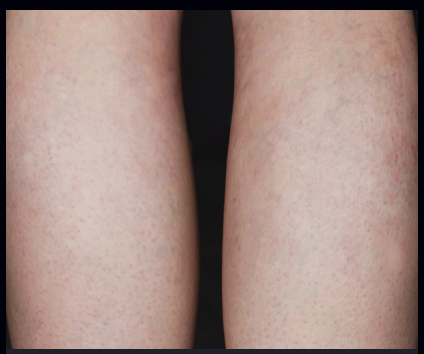

After 2 Tx

Photos Courtesy of Bienkowscy Clinic

Melasma Pathogenesis

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Disclosures: *none*

OUTLINE: Melasma is a disease with complex multifactorial pathogenic mechanisms including genetic predisposition, solar damage, barrier abnormalities, hormonal influences, transcriptional factors and inflammatory mediators.

KEYWORDS: melasma, pathogenesis, hyperpigmentation

Tran A, Nguyen D, Vaidya S. Melasma Pathogenesis. Opin Prog Cosmet Dermatol 2020;1(1):12-14.

Introduction

Melasma is a disease with complex multifactorial pathogenic mechanisms including genetic predisposition, solar damage, barrier abnormalities, hormonal influences, transcriptional factors and inflammatory mediators.[1,7]

Genetic factors

Genetic predisposition has been implicated as one of the main factors in melasma pathogenesis. However, there is high variation between family history with reported rates as high as 61%.[1] Evidence from several studies show a higher incidence in patients with darker skin types.[2,8] Downregulation of gene H19 was found in both normal and hyperpigmented skin which leads to stimulation of melanogenesis and increased transfer of melanin to keratinocytes.[1]

Other genes involved in biosynthesis of melanin include tyrosinase encoding genes (*TYR*), tyrosinase-related proteins (*TRP1* and *TRP2*), and microphthalmia-associated transcription factor (*MITF*).[4] Upregulation of *TYR*, *MITF* and *TRP1* has been observed in melasma. Wnt pathway modulation genes, prostaglandin synthesis gene (*PGE*) and genes for fatty acid metabolism also have been implicated.[1] Affected patients have reduced expression of Wnt inhibitory factors-1 (WIF-1) in epidermal keratinocytes and dermal fibroblasts which regulate melanogenesis and melanosome transfer.[1] Fibroblasts from photoaged skin also produce increased levels of pro-melanogenic factors including KGF, HGF and stem cell factor (SCF).[8]

Sun exposure

Both ultraviolet irradiation (UV) and visible light have been considered to play a role.[4] This is also supported by similar histopathological findings between melasma and chronic UV damage.[4] Visible light has been shown to induce long lasting pigmentation in melano-competent individuals. The shorter wavelengths (blue-violet) of visible light act on melanocytes through the activation of Opsin 3 (OPN3); a sensor for visible light pigmentation.[5,7,8]

Melanogenesis is stimulated both directly and indirectly. Direct stimulation of melanogenesis is caused by formation of endogenous 1,2 diacyclycerol (DAG) from melanocytes and nitric oxide (NO) production from keratinocytes which has a paracrine effect.[4] Indirect effects occur through the release of melanogenic factors which include fibroblast growth factor, sFRP2, nerve growth factor, endothelin-1 (ET1) and proopiomelanocortin-derived peptides.[8] Ultraviolet light induces production of reactive oxygen species (ROS) by activating NO synthase which also promotes melanogenesis.[2] Furthermore, UV and visible light upregulate SCF secretion through dermal fibroblast, ligand for tyrosine kinase receptor and c-kit in epidermis which leads to stimulation of melanogenesis.[2]

The distribution of melasma on specific areas that are rich in sebaceous glands (malar, forehead, upper lips) indicate that sebocytes can influence melanogenesis. Regulated by αMSH, sebocytes can synthesise vitamin D and secrete cytokines (IL-1, IL-4) and growth factors that both directly and indirectly affect melanocyte function.[8]

Hormones

Hormonal influences have a significant role in melasma pathogenesis with a higher prevalence during pregnancy, use of contraceptive pills and hormone replacement therapy.[2,8] Oestrogen and progesterone have both been implicated in the development of this condition.[4]

Melanogenesis is stimulated through the effects of oestrogen receptors on melanocytes through induction of melanogenic enzymes including tyrosinase, TRP1, TRP2 and MITF through the cyclic AMP-protein kinase A pathway. Oestrogen is also responsible for the upregulation of PDZ domain protein kidney 1 (PDZK1).[4] PDZK1 has been shown to interact with ion exchangers such as sodium-hydrogen exchange factor (NHE), cystic fibrosis transmembrane conductance regulator (CFTR) and SLC26A.[1] This interaction results in melanosome transfer and stimulation of melanogenesis.[4] Similarly, an increase in progesterone levels stimulate melanogenesis in epidermal melanocytes.[3] Both hormones are mediated by oestrogen receptors ER-alpha/ER-beta and progesterone receptors.[3]

Vascular factors

Altered dermal vasculature also has been considered in melasma. Ultraviolet light stimulates secretion of vascular endothelial growth factor (VEGF), a product from keratinocytes. This is proposed as one of the mechanisms for increased melanocyte activity through enhancement of melanogenesis.[2] It is thought to increase the density, size and dilation of vessels in affected skin.[6]

Basement membrane

Damage to basement membrane may result in migration of melanin and melanocytes into the dermis which is responsible for pigmentation. This is supported microscopically, as there is increased melanin in epidermal keratinocytes and dermal macrophages in melasma.[4]

Impaired barrier function from downregulation of lipid metabolism is found in lesional skin.[2] There is thinning of stratum corneum and flattening of rete ridges which contributes to delayed barrier recovery.

Solar elastosis

Lesional skin of melasma also consists of prominent solar elastosis due to photoaging and chronic sun exposure. Solar elastosis is the accumulation of elastic tissue in the dermis from sun and photoaging.[6] Elastotic areas have an increased histamine production by mast cells. Histamine increases melanin production through its action on H2 receptors mediated by cyclic AMP-protein kinase A activation.[4]

MicroRNA

MicroRNAs are nucleotides that express non-coding RNA which regulate transcriptional gene expression. Reduced expression of H19 RNA-derived mRNA called MiR-675 has been thought to play a role in melanogenesis and melanosome transfer.[4]

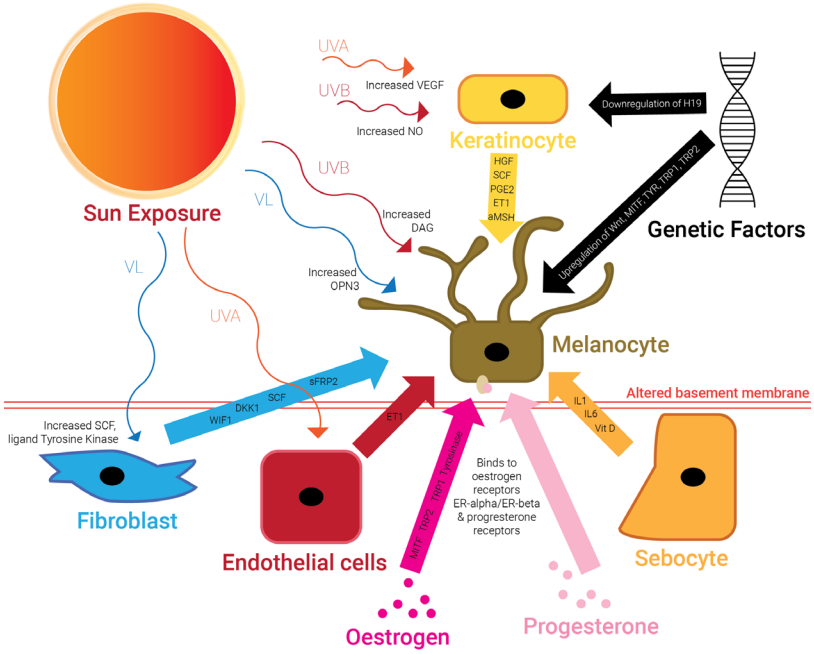

Figure 1: *Schematic diagram of factors involved in melasma pathogenesis.*

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Diagnosis of Melasma and Diagnostic Tools

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Disclosures: *none*

OUTLINE: Facial pigmentation remains a clinical challenge for all dermatologists due to similar appearance despite myriad of causes.

Facial hyperpigmentation in women is often misdiagnosed as melasma resulting in subpar clinical outcomes due to the lack of identification of the correct cause of the pigmentation and appropriately targeted treatment.

Most dermatologists will base their diagnosis on a visual examination. The characteristic appearance of melasma means that the diagnosis is usually straightforward and can be made clinically by a dermatologist.

However, Wood's lamp and dermatoscope may aid diagnosis and help determine the level of melanin deposition. More importantly, these diagnostic tools assist in ruling out differential diagnoses and facilitate appropriately targeted treatment.

The article outlines the presentations of melasma, helping amalgamate the findings and rule out common differential diagnoses.

KEYWORDS: melasma, Wood's lamp, dermatoscope

Gupta M, Doolan B, Manungo F. Diagnosis of Melasma and Diagnostic Tools. Opin Prog Cosmet Dermatol 2020;1(1):15-18

Clinical features

There are several distinct patterns of clinical presentation (Figure 1):

- Centrofacial pattern: forehead, cheeks, nose and upper lip (excluding the philtrum). This pattern is present in 50-80% of cases.
- Malar pattern: restricted to the malar cheeks and nose.
- Mandibular pattern: jawline and chin.
- Extra-facial pattern: Forearms, and the upper extremities. This pattern is often distributed in sun exposed sites and may be triggered by use of oestrogens to the forearms from menopausal hormonal therapy.

Additional variation

- Reddened or inflamed forms of melasma (also called erythrosis pigmentosa faciei).

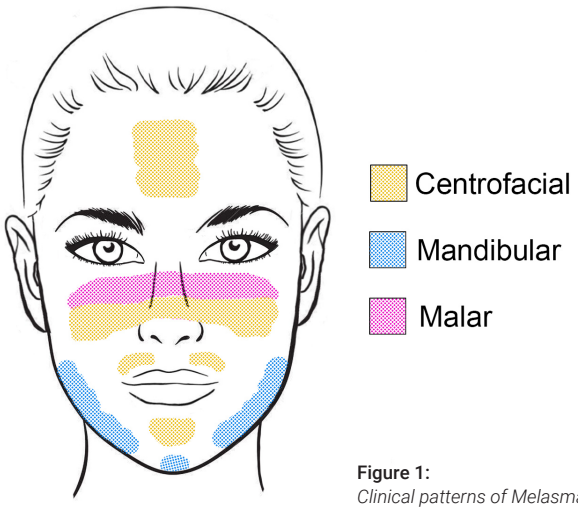

Figure 1:
Clinical patterns of Melasma

Melasma is sometimes separated into epidermal, dermal, and mixed types depending on the level of increased melanin in the skin.[1] A Wood's lamp examination and dermatoscopy can help assess the location, distribution and intensity of pigment. The findings may predict response to treatment and also help the clinician utilise strategies to direct treatment to the correct depth of the skin.

Wood's lamp examination

A handheld lamp that emits UV light in the 320-400nm range may be used to identify the depth of the pigment. The examination is usually carried out in a dark room using the lamp which emits a black light which is invisible to the naked eye but also emits some light in the violet region of the electromagnetic spectrum. The lamp is held 20-30 cm away from the skin.[3] It is recommended that patients keep their eyes shut during the examination.

Normal skin will exude a purple or violet hue.[4] Changes in fluorescence in certain skin areas can be caused by excess collagen or porphyrins as well as certain bacteria, fungi and hyper and hypopigmentation of the skin.[3, 4]

Hypopigmented skin has increased sharpness of borders and fluoresces bright white due to decreased collagen or melanin while hyperpigmented skin shows enhanced border contrast and lesions can fluoresce a wide range of colours as seen in melasma.[3]

On Wood's lamp evaluation, epidermal melasma usually shows accentuation under light and dermal shows no accentuation of light. Mixed epidermal pigmentation pattern with characteristics of both types is also observed.[2] It is important to note however that the extent of pigmentation of melasma lesions might be underestimated by Wood's lamp evaluations.[2] Furthermore, the use of sunscreen, topical agents, collagen and vascular changes as well as skin colour of the patient may all affect the Wood's lamp analysis of lesions.[2] In skin phototypes V and VI , the melasma may not be evident under Wood's lamp examination and is termed indeterminate.

Histopathological studies suggest that Wood's lamp examination may not be completely accurate as those with epidermal melasma may demonstrate some dermal pigment on histopathological examination. Nevertheless, Wood's lamp is a convenient, non-invasive, cheap, bed side tool in *estimating* pigment depth, although dermatologists inexperienced in its use may find it difficult to interpret the findings as compared to experienced users.

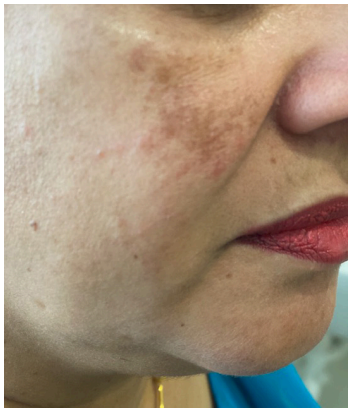

Figure 2.
Epidermal melasma (clinical)

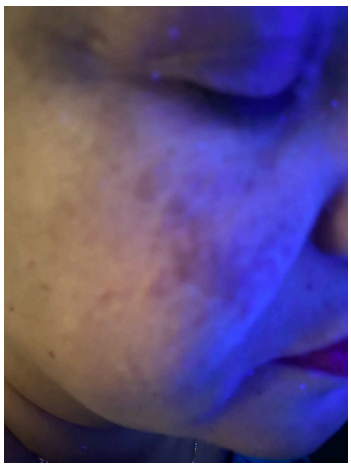

Figure 3.
Epidermal melasma (Wood's lamp)

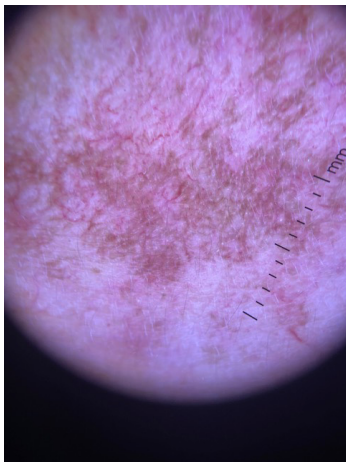

Figure 4.
Epidermal melasma (dermatoscopy) – indistinguishable from TMEP

In summary

Epidermal melasma

- Well-defined border (Figure 2)
- Dark brown/blackish colour
- Appears more obvious under Wood's lamp (worse than in natural light) (Figure 3)

Dermal melasma

- Ill-defined border
- Light brown or bluish grey
- No accentuation under Woods lamp (less discernible than in natural light)

Mixed melasma

- Combination of bluish, light and dark brown patches
- A mixed pattern is seen under Woods light with areas of epidermal and dermal findings.

Dermatoscopy

Dermatoscopic evaluation of melasma can yield significant information regarding degree of photo damage, intensity and depth of pigmentation and thereby guide treatment strategy based on the findings.

Dermatoscopic evaluation has highlighted the under-appreciated vascular component of melasma. This suggests a pathway for vasodilatation as a result of photodamage from thermal, UVR and visible light in addition to angiogenesis which may be stimulated by hormonal mediators especially oestrogen. There is increasing evidence of interaction between melanocytes and mast cells and also the pro angiogenic role of mast cells. In fact the dermatoscopy of epidermal melasma (Figure 4) may be indistinguishable from that of Telangiectasia Macularis Eruptiva Perstans (TMEP) (personal observation).

Epidermal melasma lesions shows a patchy or homogenous reticular pigment network with light to dark brown globules and granules with perifollicular sparing.[1,2] Telangiectasias and increased vascularity have also been observed.[1] The epidermal subtype of melasma shows a uniform light brown pigment distribution.

The dermal subtype is more heterogenous with grayish brown or grayish blue-black irregular pigment network that is less responsive to treatment.[1,2] Reticuloglobular pattern, telangiectasia and arciform structures may be appreciated on dermatoscopy.

Mixed subtype of melasma usually presents with a diffuse reticular pigment of grayish-black or brownish irregular patches.[2]

The depth of pigment may reflect the duration of the disease and thereby likelihood of response to treatment.

The degree of correlation in dermatoscopy and Wood's lamp findings has been shown to be substantial however, dermatoscopy remains a superior diagnostic tool that provides the added advantage of being able to observe collagen and vascular changes as well as accurately identify the subtypes of melasma presentation, based on pigment location, without influence of confounders.[2]

Histopathology

A biopsy is often refused by the patient due to the distribution of lesions on cosmetically visible sites and the increased risk of scarring in darker skin types.

Occasionally, a skin biopsy may be performed to confirm the diagnosis of melasma or rule out differential diagnoses.

Histology varies with the type of melasma, but typically the following features are noted:[1,5]

- Solar elastosis and elastic fibre fragmentation suggesting a role for photodamage
- Basement membrane disruption
- Increase in number and size of blood vessels
- Increased number of mast cells
- Melanin deposited in basal and suprabasal keratinocytes
- Highly dendritic (branched) intensely pigmented melanocytes
- Melanin in the dermis within melanophages (facilitated by basement membrane disruption)
- No difference in melanocyte number between lesions and perilesional normal skin.

Confocal microscopy

Reflectance confocal microscopy (RCM) has also been used to evaluate melasma on a cellular level. In the epidermis, hyper-refractile cobble stoning cells may be present, corresponding to hyperpigmented basal keratinocytes on histology.[1] An advantage of RCM analysis is that it can non-invasively and accurately categorize the subtype of melasma, as well as quantitate the response to therapy, however access to this is available in research centres only.[6,7]

Comprehension of the clinical and dermatoscopic findings helps us understand why epidermal melasma is more responsive to treatment while mixed and dermal melasma is more difficult to treat.

Targeting melanin alone with bleaching agents like hydroquinone will likely result in relapses due to the underlying cause i.e previous and ongoing photodamage not being completely addressed.

Laser treatments and aggressive physical therapies often worsen the disease by causing post inflammatory hyperpigmentation.

Oral tranexamic acid works on the vascular pathway which is a more upstream intervention hence is an effective treatment but not a lasting one as it fails to address the risk factors in the pathogenesis.

The effective and lasting treatment of melasma will call for a paradigm shift in the treatment strategies emanating from the use of diagnostic tools.

Common differential diagnosis for melasma

- Post-inflammatory hyperpigmentation
- Solar lentigines
- Acquired dermal macular hyperpigmentation
- Ochronosis (exogenous) from hydroquinone use.
- Discoid lupus erythematosus
- Poikiloderma of Civatte (reddish-brown patches with atrophy)
- Ephelides (freckles)
- Drug-induced pigmentation (e.g. due to minocycline or nonsteroidal anti-inflammatory drugs)
- Actinic lichen planus
- Acanthosis nigricans
- Frictional melanosis
- Naevus of Ota
- Hori's macules

Some of these conditions may co-exist with melasma as a cause of facial hyperpigmentation, both being commoner in skin of colour. However an understanding and interpretation of dermatoscopy and Wood's lamp examination finding can help understand the pathogenesis of melasma, rule out differential diagnosis and better tailor treatment strategies for management of facial pigmentation.

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Clinical Pearls: Melasma Diagnosis & Differential Diagnosis

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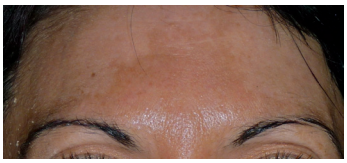
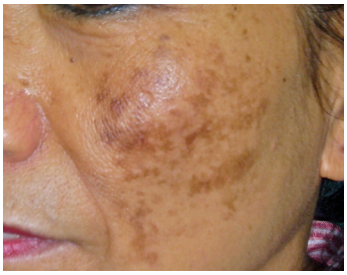
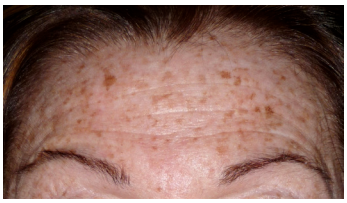
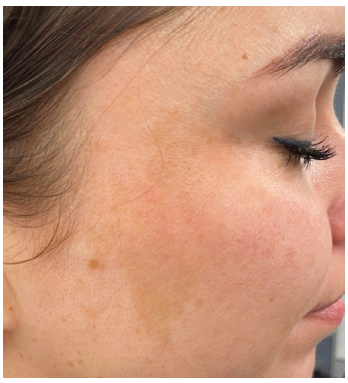
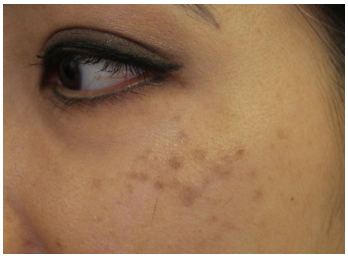
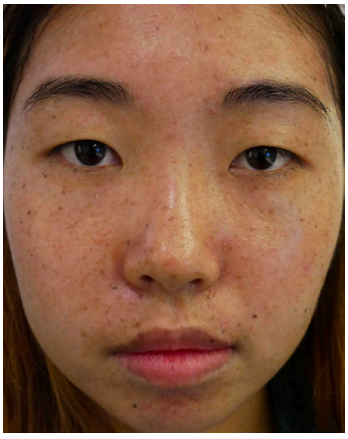
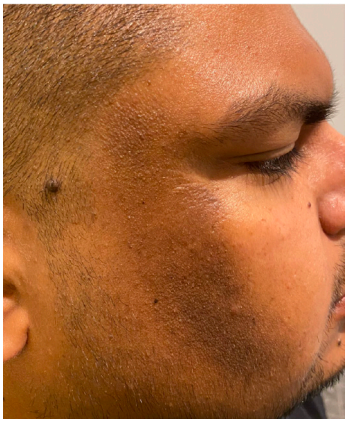
Disclosures: *none*

KEY WORDS: melasma, lentigines, pigmentation, hyperpigmentation, Hori nevus

Lim D. Clinical Pearls: Melasma Diagnosis & Differential Diagnosis. Opin Prog Cosmet Dermatol 2020;1(1):19-20.

Condition	Clinical Findings & Diagnostic Clues	
Melasma	**Irregular macules involving the lateral cheeks but classically sparing a zone surround the eyelids. Frequent involvement of the upper lip.** **Primarily Epidermal:** Wood lighting enhanced, brown in colour. **Primarily Dermal:** Wood light negative, grey macules. **Mixed:** Spotty enhancement. Mixed pattern. **Mandibular:** Jawline distribution, older age group Most commonly spotty enhancement on Wood light.	 **Figure 1.** *Melasma*
Post Inflammatory Hyperpigmentation	Areas of hyperpigmentation after the primary cause of inflammation subsides. Preceding history & distribution is often diagnostic. Pigmentation can be epidermal or dermal.	 **Figure 2.** *Post-inflammatory hyperpigmentation, post-IPL*
Lentigines	Discrete lesions with sharply demarcated and irregularly curved borders. Dermatoscopic examination shows scalloped borders, with moth-eaten appearance.	 **Figure 3.** *Lentigines*
Poikiloderma	Involves the lateral aspects of the neck, sparing the under chin area. Does not involve upper lip, nor periocular areas. Poikiloderma & melasma may co-exist.	

Condition	Clinical Findings & Diagnostic Clues	
Pigmentary Demarcation Lines	Sharp well demarcated lines arising from the lateral orbit. Onset in adolescence.	 **Figure 4.** *Demarcation lines*
Hori Naevus	Naevus of Hori are melanocytic naevi that have a slate-brown or blue/grey colouring. They form discrete periocular macules however do not affect the upper lip. Dermatoscopic signs include brown to grey discrete structureless areas signifying dermal pigmentation. No increase in lesional telangiectasia compared to melasma. Can be challenging to differentiate between dermal melasma & Hori naevi as both may coexist.	 **Figure 5.** *Hori Naevus*
Freckles	Discrete macules, involving the nose, but sparring the upper lip. Fluctuation with UV exposure. Dermatoscopy shows uniform pigmentation and a moth-eaten edge.	
Xeroderma pigmentosum	Extensive solar pigmentation at an early age. Macules on the lips, exposed areas including the face, neck, chest & dorsal aspects of the hands.	 **Figure 6.** *Xeroderma pigmentosum*
Drug induced pigmentation	Based upon history & distribution. Frequently implicated drugs include minocycline & NSAIDs. May localize to scars.	
Other – e.g. Acanthosis nigricans	Velvety pigmentary change to the skin on flexural areas (and face) with a predilection for darker skin types. May be associated with obesity/ insulin resistance and rarely, malignancy.	 **Figure 7**. *Acanthosis nigricans*

Clinical Pearls: Melasma Management

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KEY WORDS: Melasma, melasma treatment

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Managing Melasma

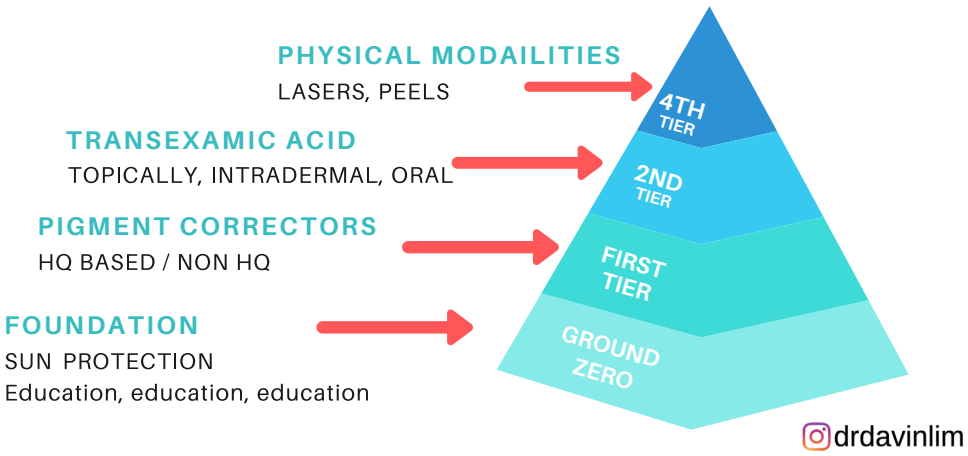

Figure 8. *Managing melasma (pyramid)*

Strategy	Comments
Foundation of management, photoprotection Broad Spectrum Sunscreens. Adjunctive broad brimmed hat, umbrella, window tint for vehicles.	Patient education regarding strict & absolute photoprotection & correct use of sunscreen forms the foundation of melasma treatment. Incidental UV exposure via daily commute is often overlooked.
First Line Topicals Hydroquinone (HQ) 2-8%	Titrate concentration according to skin sensitivity. Stability of formulation is important as HQ is both heat & light labile. Stand alone formulations allow titration compared to Kligman's formulations. HQ should not be used for periods longer than 4 to 6 months.

Strategy	Comments
Second Line Topicals Tretinoin Ascorbic acid Azelaic acid Arbutin Botanicals AHAs Kojic acid Cysteamine	The use of botanicals & novel compounds such as cysteamine can be useful for rotational therapy. Kojic acid concentration should be 1-2% to decrease incidence of contact dermatitis.
Adjunctive Treatments – Lasers	Low fluence 1064nm NdYag Q-Switch Dermal Toning can give good results with low risks. Sessions should be spaced a minimum of two weeks apart to reduce incidence of permanent guttate hypopigmentation. Picosecond lasers can be effective however post-inflammatory hyperpigmentation & melasma flare ups are more common compared to nanosecond lasers. Fractional 1927 Thulium & diode lasers are promising. Pulse dye, KTP & copper bromide lasers can effectively address the vascular component of melasma.
Systemic oral agents – Tranexamic acid	In the absence of contraindications, oral tranexamic acid in doses ranging from 250 mg to 500 mg should be considered as adjunctive treatment. Though the efficacy of tranexamic acid has been demonstrated in many papers, it still remains as off label for the management of melasma & post inflammatory hyperpigmentation.
Adjunctive Treatments – Peels	Novel peeling agents can be useful in the management of epidermal melasma. Superficial peels including retinoic acid, AHA peels & low concentration TCA (10-15%) can be useful adjunctive treatments.
Novel Treatments – Microneedling	Though reported in the literature for the treatment of many skin conditions, microneedling (with or without PRP) has limited value.

Management of Melasma: Current Recommendations

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OUTLINE: Melasma is an acquired disorder of facial hyperpigmentation commonly presenting in women and in those with skin of colour. It is a chronic relapsing disorder that can have a significant impact on the quality of life. It also presents a considerable therapeutic challenge to the practitioner.

The management of melasma requires a multimodal approach underpinned by strict adherence to long-term photoprotection. A diverse range of topical therapies, chemical peels and light or laser therapies have also been trialled with varying evidence and efficacy. This article provides an overview of the existing and emerging therapies for melasma with the strongest evidence and aims to provide current recommendations for the practicing dermatologist.

KEYWORDS: melasma, pigmentation, hydroquinone, tranexamic acid, hyperpigmentation

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Introduction

Melasma is a chronic acquired pigmentary disorder of the face, more commonly affecting adult women.[1] The prevalence of melasma varies among different cultural groups corresponding to varied skin types, predominantly affecting females and skin of colour (non-Caucasian skin, typically Fitzpatrick skin type IV-VI).[2]

Several risk factors implicated in the development of melasma, including: pregnancy; exogenous hormonal therapies; exposure to ultraviolet (UV) radiation, heat and the visible light (VL) spectrum; vascular modulation; and genetic or familial predisposition.[3,4]

Clinical features

Melasma presents clinically as a pattern of hyperpigmented light- to gray-brown macules or patches in the central, malar or mandibular regions of the face.[2] Examination of hyperpigmented areas under a Wood's lamp may help assess the layer of pigment deposition (epidermal, dermal, mixed or undiscernible).[2]

Histopathological examination of melasma demonstrates increased melanin in the epidermis and dermis, and features of photoaging – including solar elastosis, mast cells, vascularisation and altered basement membranes.[5] There is a broad range of possible differential diagnoses for facial pigmentary disorders, including: naevus of Ota; Hori's naevus; medication-induced hyperpigmentation; acquired dermal melanosis and exogenous ochronosis. A skin biopsy can be helpful in discerning melasma from other conditions.[1]

MASI & mMASI scoring of severity

The Modified Melasma Area and Severity Index (mMASI) score is a validated measure of melasma severity and is commonly used as an outcome measure to quantify changes in melasma during treatment.[6] It is calculated by rating the darkness and percentage of involvement of four areas of the face (forehead, left malar, right malar and chin region).[6] The mMASI removes the "homogeneity" factor used in the original MASI while maintaining accuracy and improving usability.

Management

Counselling

It is important in early counselling to set initial patient expectations. Melasma is a recalcitrant condition that cannot be cured and recurs in every patient. The management of melasma is never via monotherapy. It requires combination rotational therapy, which is determined on a case-by-case basis and is dependent on location, type and duration of melasma. Furthermore, the clinician must recognise and explore the emotional impact for the patient, with counselling from allied health colleagues if needed.[7]

Lifestyle changes

The cornerstone of treating melasma is maintaining strict year-round photoprotection, as UV and VL exacerbates melasma and can induce relapses.[8] This includes: physical coverage (wearing a broad-brimmed hat, 100% UV-blocking sunglasses, long-sleeved clothing); applying broad-spectrum tinted sunscreen; seeking shade and sun avoidance (especially during high UV times from 10am to 3pm); and avoidance of artificial UV sources (such as tanning salons).[1, 3, 8]

Other cosmetic camouflage with commercially available make-up foundation and concealer is often used as an effective interim solution.

Topical agents

Topical therapies for melasma pharmacologically target the melanin synthesis pathway, which involves the conversion of L-tyrosinase to L-DOPA (L-3,4-dihydroxyphenylalanine) by tyrosinase and the conversion of L-DOPA to melanin.[2]

The first line of treatment consists of a short course of topical agents, often used in combination therapies, under the guidance of a qualified dermatologist.

Hydroquinone (HQ) (1,4 dihydroxybenzene) used in a 2-5% stabilised emollient acts as an effective topical depigmenting agent by competitively inhibiting the conversion of L-DOPA to melanin. It has been the gold-standard first line therapy for epidermal melasma for over 50 years.[1] Short-term adverse effects are commonly local and dose and duration dependent – including erythema, stinging, xerosis, irritant or allergic contact dermatitis and transient halo hypochromia.[1, 9] Long-term effects (often mitigated by short-term use) include milia, paradoxical PIH, confetti-like depigmentation, and rarely, exogenous ochronosis (a black-blue pigmentation that develops secondary to depigmenting phenols).[10] It is contraindicated in those that are pregnant or breastfeeding.

Topical retinoids are vitamin A derivative preparations that have been effectively used to treat a range of dermatological conditions including melasma. Proposed mechanism of action includes inhibiting tyrosinase transcription and melanin synthesis, stimulating epidermal keratinocyte metabolism and facilitating penetrance of other active ingredients. However, retinoids are cutaneous irritants (causing erythema and desquamation) and known teratogens (therefore also contraindicated in pregnancy).[11, 12]

Tretinoin is a potent topical retinoid that has been found to be effective in treating epidermal melasma (with a 32-37% improvement in MASI), especially used in combination therapy.[11, 12]

Adapalene is a synthetic retinoid, which has also proven to be an effective formula for melasma (41% reduction in MASI) with less cutaneous irritation than tretinoin.[12]

Azelaic acid (AA) 20% is a *Pityrosporum ovale* derivative and functions as a competitive tyrosinase inhibitor, with a similar response to 4% HQ for epidermal melasma, however has more significant adverse effects than HQ especially at higher concentrations.[10] It can be used in pregnancy and during lactation.

Other topical agents that have been trialled for melasma include 60% kojic acid (tyrosinase inhibitor), 25% ascorbic acid (vitamin C), 3% arbutin (or deoxyarbutin), niacinamide (vitamin B3), 2-5% topical tranexamic acid, licorice extract (melanin dispersion, tyrosinase inhibitor), rucinol 0.3% serum (phenolic acid derivative tyrosinase inhibitor), dioic acid, linoleic acid 2% and methimazole. However, these have demonstrated only limited efficacy, are unstable as monotherapy, or have more significant adverse effects than current treatments.[1]

Combination topical therapies

Hydroquinone and retinoids are often used in combination formulas to synergistically treat moderate to severe melasma. The Kligman-Willis formula (KF; 5% hydroquinone, 0.1% tretinoin, 0.1% dexamethasone) was one of the earliest therapies, which evolved to become the Modified Kligman's formula (MKF; 4% hydroquinone, 0.05% retinoic acid, 0.1% betamethasone).

Multiple other formulas exist, but the most extensively researched combination is the triple combination cream (TCC; 4% hydroquinone, 0.05% tretinoin and 0.01% fluocinolone acetonide), which has demonstrated superior efficacy compared with monotherapy[13] or dual therapy[14]. TCC is commonly available as a compounded formula, or in some countries, as a commercial preparation (TriLuma® in USA). When used with photoprotection, it achieved near-complete clearance in 77% of participants in an investigator-blinded randomised trial compared with dual combination formulas.[14] TCC can be applied nightly for 8 weeks, with a maintenance twice-weekly application thereafter. Adverse effects include local reactions as aforementioned for the separate components, however it is thought that by combination with retinoid, TCC mitigates the risk of skin atrophy from corticosteroids.[14]

Emerging topical therapies

Cysteamine (an aminothiol) in a 5% cream is a potent depigmenting agent, applied once daily for 15 minutes. It is hypothesised to inhibit a number of enzymes and substrates in the melanin synthesis pathway, with a good safety profile.[15] Previously, oxidized cysteamine emitted an odour that rendered it unsuitable for topical use. In 2010, the formulation of cysteamine was

stabilised and deodorised for use, with clinical trials demonstrating that cysteamine was effective in treating epidermal melasma,[16] and potentially more effective than MKF.[15] Further studies are required to demonstrate sustained efficacy and safety, but early results from a number of studies suggest cysteamine may be helpful for melasma.

Systemic agents

Tranexamic acid (**TXA**) is an antifibrinolytic agent inhibiting plasmin that is traditionally used for menorrhagia and other bleeding diatheses, with a history of off-label use for melasma, angioedema and urticaria.[17] TXA is proposed to inhibit the UV-induced plasminogen/plasmin system, subsequently hindering melanocyte-keratinocyte interaction, which in turn reduces tyrosinase activity and melanogenesis.[5]

Improvement in moderate melasma has been demonstrated after three months of TXA 250 mg twice daily, with recurrence noted in severe melasma.[5] TXA can assist the efficacy of topical hydroquinone when used in combination.[9]

Overall TXA is reported to be effective and well-tolerated.[5] However, side effects can include headaches, nausea, menstrual irregularity and back pain as well as arterial and venous thromboses.[17] Contraindications include cardiovascular, respiratory or renal disease, previous thrombosis, or concurrent use of prothrombotic medications.[9]

In the absence of larger-scale trials, oral TXA has been suggested as a third line treatment for severe, recalcitrant melasma.[17]

It is the belief of the authors that tranexamic acid should not be used during the COVID-19 pandemic, especially in those who have higher chances of contracting or suffering complication of COVID-19. This is due to the prothrombotic events that have been reported in even young and otherwise healthy individuals who are infected with COVID-19.[18] Given the mechanism of action, TXA should be avoided in these cases.

Chemical peels

Chemical peels are a common adjunct to topical agents, used to induce controlled exfoliation and subsequent regeneration of the epidermis and dermis. They have greatest efficacy in epidermal melasma. A peeling regimen includes photoprotection, pre-treatment or priming (often with hydroquinone), peel and maintenance with 5-6 sessions at 2- to 4-week intervals. Each component must be carefully chosen to optimise the efficacy of the peel and reduce the risk of PIH. Post-peel maintenance emphasises sun protection and a regimen for continued topical therapy.[19]

Glycolic acid (GA) at concentrations of 20-70% is the most commonly used alpha hydroxyl acid as a serial peel, however there is no significant benefit in using GA compared with hydroquinone treatment alone.[20] Trichloroacetic acid (TCA) 10-20% peels have demonstrated good short-term efficacy in lighter skin but has a risk of PIH and scarring in skin of colour.[21]

Salicylic acid (SA) is a beta hydroxy acid peel used at 20-30% concentrations, with an anti-inflammatory and diffuse depigmenting effect. Its studies in melasma have been limited but it appears to have a superior safety and efficacy profile to GA peels.[22] Jessner's solution is a combination peel (14 % salicylic acid, 14 % lactic acid, 14 % resorcinol in alcohol) that has not been shown to be significantly different.[22]

Other trialled peels include lactic acid, phytic acid, pyruvic acid, tretinoin peels, combination salicylic acid and madelic acid, however there is limited evidence for efficacy.

Laser and light therapies

Laser and light therapies can be considered as last-line treatments for refractory, severe melasma. Like chemical peels, they should be used cautiously in skin of colour due to the risk of inducing paradoxical PIH, worsening melasma and scarring. Other adverse effects include mottled confetti-like hypopigmentation, irritation and recurrence post-treatment.[23,24]

Different modalities have been trialled to treat melasma with variable and limited evidence. These include intense pulsed light (IPL) (560 nm),[23] broad band light (BBL), QS ruby laser (694 nm), non-ablative fractional laser (1550 nm), Q-switched neodymium-doped yttrium–aluminium–garnet laser (1064 nm) (QS-Nd:YAG laser or 1064 QNYL),[24] Pulsed-dye Laser (PDL), erbium glass non-ablative fractional laser (1550 nm) and Erbium:YAG ablative laser (2940 nm). They also carry a greater risk of erythema, irritation, recurrent and post-inflammatory hyperpigmentation.

The laser therapy with the greatest evidence base for efficacy for treating pigment is the Picosecond Alexandrite Laser (755-nm) (PicoSure® by Cynosure). When used at a 755 nm pulse duration, the picosecond alexandrite photomechanically targets melanin, with a lower photothermic effect which minimises damage to surrounding tissue and therefore reduces adverse effects.[25] It has been shown to have significantly greater pigment clearance rates when compared with 1064 QNRL in a split-faced study, with minimal side effects.[25] While there are now picosecond 1064NdYag lasers available, scientific evidence of their efficacy is lacking at this time.

Conclusion

The management of melasma requires a multifaceted long-term approach. Initial consultation should confirm melasma, assess clinical severity and address risk or exacerbating factors. The first principles of management – avoiding triggers and strict year-round photoprotection with tinted sunscreen – should be emphasised. Cosmetic camouflage can be an immediately effective temporary measure.

Mild melasma can be treated with a short course of daily hydroquinone 2-4% cream, the gold-standard topical depigmenting agent. Inadequate response or moderate to severe cases of melasma can be treated with a short course of daily combination or triple combination cream. Refractory cases may warrant escalation to short courses of intermittent chemical peels or a short course of systemic treatment. Laser or light therapies can be considered as a last-line treatment in recalcitrant severe melasma, with the Picosecond Alexandrite Laser (755 nm) being the preferred technology at this time. Any course of treatment should be individualised and carefully monitored for relapse and cutaneous adverse effects.

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Cosmeceutical Agents in Melasma

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Melasma remains a challenging condition for the physician to treat. It affects both men and women of all ethnicities and Fitzpatrick skin types and is considered universally undesirable from an appearance perspective. The available treatments for melasma focus on photoprotection from UVA, UVB, IR, and visible light; all of which can increase skin pigmentation. However, there is a need for pigment lightening beyond the use of sunscreens. The gold standard for melasma treatment has been hydroquinone, but recently the safety of this ingredient has been called into question.

Hydroquinone, a phenolic compound chemically known as 1,4 dihydroxybenzene, functioning to improve facial pigmentation by inhibiting tyrosinase, is the rate-limiting enzyme in melanin pigment production. Hydroquinone covalently binds to histidine or interacts with copper at the active site of tyrosinase inhibiting RNA and DNA synthesis and altering melanosome formation. These activities suppress the melanocyte causing gradual decrease of melanin pigment production. The safety of hydroquinone has recently been called into question, as the ingredient may be toxic to melanocytes, instead of simply suppressing melanin production.[1] This concern has led to the search for cosmeceutical agents that can be used for the treatment of melasma.

Many physicians try to limit the hydroquinone concentration to 2%, which is the over-the counter (OTC) drug concentration allowed in the US, but not in Asian countries where the substance is considered illegal. Combining hydroquinone with cosmeceutical OTC vitamin A formulations, such as retinol or retinaldehye, may improve the irregular grouping of melanocytes,[2] which can be normalised with retinoids. While this effect is more dramatic with topical prescription tretinoin, topical OTC retinol has been thought to provide similar effects.[3]

The cosmeceutical ingredient most similar to hydroquinone is kojic acid. Kojic acid, chemically known as 5-hydroxymethyl-4H-pyrane-4-one, is a hydrophilic fungal derivative obtained from *Aspergillus* and *Penicillium* species. The activity of kojic acid is attributed to its ability to prevent tyrosinase activity by binding to copper.[4] However, kojic acid needs to be penetration enhanced and may also be melanotoxic, which is why it is no longer allowed in cosmeceutical formulations in Asia.[5]

The most widely used cosmeceutical ingredient for melasma treatment are the licorice extracts liquiritin and isoliquertin, which are glycosides containing flavenoids.[6] Liquiritin *in vitro* induces skin lightening by dispersing melanin. Two other pigment lightening cosmeceutical ingredients are aleosin and arbutin. Aleosin is a low-molecular-weight glycoprotein obtained from the aloe vera plant. It is a natural hydroxymethylchromone functioning to inhibit tyrosinase by competitive inhibition at the DOPA oxidation site.[7] It is sometimes mixed with arbutin, obtained from the leaves of the Vaccinicum vitis-idaca plant, which is a naturally occurring gluconopyranoside that causes decreased tyrosinase activity without affecting messenger RNA expression and inhibits melanosome maturation *in vitro*.[8]

Finally, vitamin C is used in some cosmeceutical formulations as a pigment lightening active for its ability to interrupt melanin production by interacting with copper ions to reduce dopaquinone and blocking dihydrochinindol-2-carboxyl acid oxidation. The concentration of vitamin C must be relatively low, however, as it can easily lower pH and cause cutaneous irritation.[9]

Thus, there are a number of cosmeceutical agents to assist in the treatment of melasma, but none work in all patients. Generally best results are achieved by combining as many treatment modalities as possible until a good clinical result is achieved.

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Devices in the Treatment of Melasma

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OUTLINE: Melasma remains a difficult to treat dermatologic condition. A variety of lasers and light sources have been used over the years with success in treating melasma. Lasers and light sources can be considered in the treatment paradigm for patients with melasma with the understanding that we are treating melasma, not curing it.

KEYWORDS: melasma, intense pulsed light, fractional lasers, Q-switched lasers, picosecond lasers

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Introduction

Melasma remains one of the more difficult skin conditions we, as dermatologists, face on a daily basis in our clinics. It also is one of the more difficult skin concerns that patients have when confronted with melasma. Many times patients are misled by advertisements on skin care routines or by healthcare providers who have told them in one fashion or another, that their magic skin care or chemical peel process, or some energy based device, will "cure" their melasma. We all know that this will not be the case with what is available in today's armamentarium. One of our most important "jobs" in our assessment of the patient with melasma is to educate them on the causes of melasma. Many of these causes we can do nothing about, we can work with them on any of the causes that we can change if possible. We need to make sure that patients understand that we have no cure for melasma. Although great treatments and sun protection if done properly, can, in many, result in remission of the disease, as long as the factors that are associated with melasma are not brought back into the fold.

We are always seeing patients who we have treated return to our offices after a beach or sun holiday and are amazed that their melasma has returned. Even with our education, patients still do not understand this all the time. So we must continue the education process with our patients, even as we treat and reduce their hyperpigmentation.

We do have a myriad of treatment options available for those suffering from melasma. This issue of *Opinions and Progress in Cosmetic Dermatology* will provide you with skin care ingredients that work to inhibit the production of tyrosine; peeling agents to do the same; in addition to lasers and energy based devices (EBDs). EBDs have really helped us control some of the tougher cases of melasma that are seen in our clinics.

Treating melasma with EBDs requires an understanding of the type of melasma we are treating and a thorough understanding of the devices that one is using. An intense pulsed light (IPL) is very different than a Q-Switched or Picosecond laser. Knowing the differences between these different machines and how they interact with the targets they are reaching, is very important. So, let's review the main EBDs currently being used for the treatment of melasma.

Lasers & Light Sources

First, IPLs can work on clearing melasma. These flashlamp devices are not a true laser and work through what are called cut-off filters to target the chromophores one is attempting to interact with. When treating melasma, or pigment, many published studies have shown the benefits of the IPL in improving the skin, even in darker skin types.[1,2] Li et al. evaluated 89 Chinese women with melasma and found that 77.5% had a 51-100% improvement in their melasma following a series of 4 IPL treatments at 3 week intervals. MASI scores decreased from 15.2 to 4.5 during the course of the study. They found that epidermal melasma responded better than mixed-type melasma.[1] In another study by Feng et al., 58 patients treated with the IPL showed an 84.6% improvement in their pigment.[2]

Q-Switched Lasers (QSL) have long been an important EBD in the treatment of melasma. Early on, it was noted that rebound or recurrence with these devices were high when "common" settings for pigment were utilised. It was then found, that if the QSL was used at low fluences, with multiple treatments, significant

improvements could be reached and maintained. Several studies with regard to the low fluence QSL show its effectiveness. Wattanakrai et al. performed a split face randomised clinical trial where patients received either 5 weekly treatments of low fluence QSL and 2% hydroquinone versus 2% hydroquinone alone. The investigators found that improvement in relative lightness improved more on the QSL treated side – 92.5% versus 19.7%. MASI score improved as well - 75.9% to 24% - on the QSL group. Adverse events were seen in some with mottled hyperpigmentation and all the patients had recurrences noted over time. Most, however, were less than baseline.[3] Hofbauer Parra et al. evaluated 20 Brazilian women with melasma using a QSL. The patients received 10 weekly treatments and there was a decrease in MASI scores from 7.85 to 4.33 (P<0.001). Again, however, 81% of the patients had recurrences at 3 months following the last treatment.[4] Zhou et al., reported their findings with the QSL. Fifty patients were treated for nine weekly sessions with low fluence QSL. The melanin index in these patients went from 70 to 44.9 (P<0.001); the MASI scores decreased by 61.3% (P<0.001); 10 patients had 100% clearance as well. At 3 months following the last visit, 64% of the patients had a recurrence noted.[5] In 2014, Gold et al. reported their findings with a fractional QSL in patients with photodamaged skin and pigmentary concerns in 10 patients. The patients underwent 4 sessions of low fluence QSL at 2-4 intervals and were followed for 1 and 3 months post their last laser treatment. Hyperpigmentation improved by 70% in this patient population at 3 months post the last treatment.[6]

Fractional lasers have become very important in recent years in treating a variety of skin concerns, including pigment and melasma. Several investigators have looked at both non-ablative fractional lasers (NAFL) and ablative fractional lasers (AFL). The NAFLs consist of devices that use wavelengths from 1440 nm to 1550 nm. Rokhsar and Fitzpatrick reported their experience with the 1550 nm NAFL and found that 6 out of 10 patients with recalcitrant melasma had 75-100% clearance at 3 months after 4-6 NAFL treatments.[7] Lee et al. also worked with the 1550 nm NAFL. Twenty-five patients received 4 treatments and they showed a 60% improvement, which decreased to 52% at 6 months.[8] Kroon et al. studied the 1550 nm with triple combination cream versus the triple combination cream alone. There was overall better satisfaction with those who received the NAFL and the cream versus the cream alone.[9] Wind et al. performed a split face study using the NAFL 1550 nm device with triple combination cream versus the triple combination cream alone. The physician global assessment and the patient satisfaction scores were significantly better with the laser treated side; however, in this study, 31% of patients did develop post-inflammatory hyperpigmentation (PIH).[10] Tourlaki et al. studied the 1540 nm device in 76 patients. At one month, 67.1% had greater than 76% clearing and 21% had 51-75% clearing. At six months, only 21.1% maintained improvement, even with triple combination cream.[11]

The newest of the NAFL is the 1927 nm thulium laser. It has a greater absorption coefficient for water compared to the other NAFL lasers. It has a deeper penetration than the others, making it potentially more efficient at treating pigment. Polder and Bruce evaluated 14 patients with the 1927 nm laser, 3-4 sessions at one month intervals. The patients had some erythema, edema, and microcrusts which lasted 3-7 days after the treatment. There was no scarring or PIH noted. MASI scores improved 51%, 33%, and 34% at 1, 3, and 6 months after the last laser treatment.[12] Lee et al. performed a split face 1927 nm study on 25 Asian females (8 with melasma). The MASI scores improved 33% at 2 months versus 5% on the control side and at 6 months, the improvement was 28% versus 12%.[13] Niwa Massaki et al. looked at long term efficacy with the 1927 nm NAFL. A 12-month review of 20 women were evaluated; patients received one laser treatment and were given 4% hydroquinone one month later. Sixty percent had more than 50% clearance at one month and the MASI scores continued to improve to 53.8% at 6 months. At 12 months, there was 33% partial recurrence noted and 13% had complete recurrence.[14] Bae et al. reported their experience with 61 patients with PIH who were treated with the 1927 nm NAFL at low fluences; and with a minimum of two laser treatments, they found that there was a 43.24% improvement in pigment.[15] It should be noted that there is a combination 1550 nm/1927 nm laser system available which shows great promise in further improvements in pigmentary concerns.

AFLs have also been used in the treatment of melasma and pigmentary concerns. While there is no question that using AFLs will work in treating melasma, there is also no major doubt that recurrences and PIH can occur commonly after their use. This was shown in a study by Trelles et al. who evaluated 30 patients using either a triple combination cream versus the cream and a fractional CO_2 laser. The combination worked better than the cream alone; long term PIH was evident in many.[16] For these reasons, AFL are not considered first line in the treatment of melasma.

Picosecond lasers have been found to be successful in treating melasma by many. Again, one must understand that even with a picosecond laser, this is only a treatment and not a cure. Kung et al. reported on 12 patients treated with a picosecond laser in Asian patients with benign pigmentary lesions, including melasma. Twelve subjects were evaluated after the last laser treatment and at 4, 8, and 12 weeks following the last laser treatment. Three months after the last laser treatments, they found 53.8% of all pigmented lesions achieved an excellent response (75-94% lightening); 30.8% showed good response (50-74% lightening),

7% fair (25-49% lightening), and 7% poor (0-24% lightening). For melasma, 4.5 sessions on average was needed to achieve the results. The PIH rate was low.[17] Many other reports have shown similar data for the picosecond laser. Because of its pico nature, we assume that we may end with less treatment sessions than conventional QSL. This is one of the main advantages for the use of picosecond lasers.

Two other laser systems should be mentioned when discussing melasma. First, the Pulsed Dye Laser (PDL) has been used successfully in patients with melasma. Many think a vascular component may be involved in the pathogenesis of melasma, so it makes sense that if that is the case, then the PDL may be useful. Passeron et al. reported their experience with the PDL and a triple combination cream in a split face clinical trial of 17 patients. Clinical improvement was seen in both groups, but much more so in the PDL side. The role of vascular endothelial growth factor and its role in melasma is still being determined.[18]

The short-pulsed (650 microsecond) QSL also needs to be discussed in this manuscript. Gold et al. published a review of this laser in 2017 which showed its excellent effects on pigment and melasma. This device is contactless and also virtually painless.[19]

Conclusions

There are many devices that can be used to treat melasma. Again, we must remember that we are only treating melasma with devices, not curing it. One needs to make sure that the patient is aware of this and does not leave one's clinic thinking that once the treatments are completed, their melasma may not soon return. It is crucial for all our EBD treated patients to be on a proper skin care routine to enhance the EBD treatments and to use sun protection always following their treatments. A maintenance program should be discussed and arranged with the patient at the time of their treatments. It is important to further solidify to patients that with maintenance, we are not curing melasma. That we can use the maintenance times to continue to keep the patient in good compliance and to keep the areas of pigment, as clear as possible.

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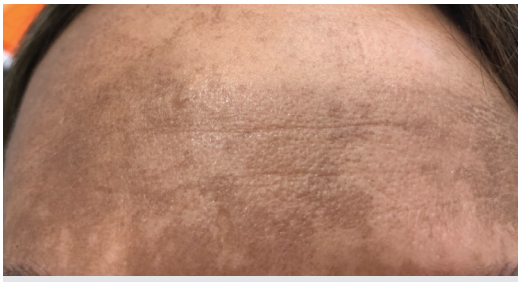

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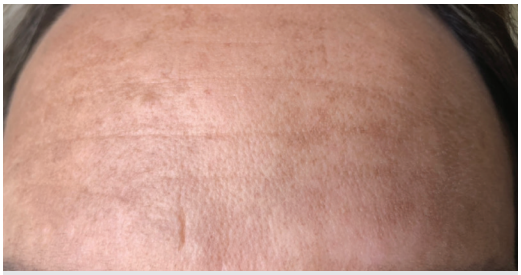

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The Great Melasma Debate: The Case for Topical Therapy

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KEYWORDS: melasma, hydroquinone, tranexamic acid, lasers, hyperpigmentation

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All dermatologists will accept that melasma is fundamentally a medical condition that can be controlled but not cured. Melasma is not dissimilar to psoriasis, a chronic condition with both medical and physical therapies. Therefore, melasma should ideally be managed with topical therapy – a modality that is consistently cheaper, safer and less likely to worsen melasma or provoke rebound pigmentation compared to many device-based therapies.

The current Cochrane review (2010) on interventions for melasma included only topical and systemic therapy but no devices, as the inclusions were limited to randomised controlled studies, which would have excluded most device-based studies.[1] All recent therapeutic reviews on melasma favour topical therapy over devices including the most recent by McKesey et al. with the conclusion: "Hydroquinone monotherapy and triple combination cream (hydroquinone, tretinoin, triamcinolone) are the most effective and well-studied treatments for melasma, whereas chemical peels and laser- and light-based therapies are equal or inferior to topicals, but offer a higher risk of adverse effects."[2]

Only the most ardent laser-enthusiast will promote devices as first-line therapy for melasma. History shows that device hype invariably exceeds therapeutic results and this is well-illustrated by the landmark 2005 'Fraxel study' demonstrating 60% of subjects (n=10) achieved 75 to 100% melasma clearance with 1 case of post-inflammatory hyperpigmentation (PIH).[3] Somewhat surprisingly, there is even a 2015 paper supporting the use of fully ablative Erbium lasers for melasma.[4] Today, we are considerably more circumspect when managing melasma and regard topical therapy as first-line intervention, and when devices are introduced, topical therapy is often recommended pre- and post-device to manage the risk of PIH and for optimal results.[5,6]

Devices show mixed results with melasma and any initially favourable outcome can become complicated by either paradoxical pigment anomalies or troublesome rebound pigmentation.[5] The use of Q-switched 'laser toning' – initially so promising for melasma – was subsequently found to cause confetti hypopigmentation, which somewhat curbed enthusiasm for this modality. Wattanakrai's split-face randomised study comparing 2% hydroquinone versus combination Q-switched 1064nm and hydroquinone (n = 22) reported 13.6% subjects with hypopigmentation, 18% with rebound hyperpigmentation and 100% melasma recurrence with time.[7] Admittedly, low fluence, larger spot size and a multi-session regimen may have ameliorated the hypopigmentation issue but this 'learning curve' pattern will always be a cautionary feature of devices and serves as a warning in regards to the new crop of picosecond lasers.

At their best, devices may produce faster melasma clearance over topicals, but this efficacy differential disappears with time. A comparative study between 1550 nm fractional laser (4 sessions fortnightly intervals) versus daily topical therapy (hydroquinone 5%, tretinoin 0.05%, and triamcinolone acetonide 0.1% cream) for 8 weeks showed higher satisfaction rate in the laser group at 3 weeks but most patients preferred topical treatment at 6 months,[8] most likely because of "extra pain for no extra gain". There appears to be little cost-benefit analysis of laser treatment – is the extra cost worth the temporary gain?

In cases of melasma refractory to topical therapy, oral tranexamic acid (TA) has emerged as a strong contender for second-line therapy.[9] Bala et al. advocated oral TA for hydroquinone resistant melasma,[10] thereby possibly relegating devices to end-of-line therapy. Arguably, if devices are ever considered, they should be last resort and adjunctive to topical therapy, on the basis of safety, efficacy and cost-effectiveness.

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The Great Melasma Debate: The Case for an All-inclusive Approach to Maximise Patient Outcomes and Satisfaction

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KEYWORDS: melasma, laser, pigment, hyperpigmentation

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Patients with melasma often suffer from low self-esteem.[1] Topical treatment traditionally involving versions of Kligman's formula with triple therapy is considered gold standard; however, there are patients who fail to respond adequately.[2] A review of studies using topical treatment showed a reduction in pigmentation ranging from 50 to high 90%.[2] Being such a difficult condition to treat and maintain, a combination approach is warranted – topical, oral and energy-based device interventions.

It is essential to consider all treatment modalities to optimise patient care, outcomes and, ultimately, satisfaction in what can be a debilitating, chronic medical condition. If we consider that we use topical and physical therapies to treat other chronic dermatological conditions such as psoriasis, why avoid them in melasma?

We acknowledge that every case of melasma is different. Skin phototype, distribution, dermal vs epidermal melasma, co-morbidities, medications, patient lifestyle and expectations, risk of developing post-inflammatory hyperpigmentation (PIH), and budget are just some of the factors that the clinician needs to consider. Therefore we must be aware of all the different possible combinations of treatment that will best take the factors into account.

The argument for topical treatment has been made previously and there is little disagreement with regards to its use in melasma. We would argue, however, that failing to consider oral and energy-based device interventions is doing a disservice to our patients. Oral tranexamic acid is becoming more popular to aid in the treatment of melasma. The vascular component to the pathogenesis of melasma is becoming increasingly evident.[3-5] Tranexamic acid works to inhibit the plasminogen/plasmin pathway thereby reducing melanin synthesis and possibly reduces vascular endothelial growth factor (VEGF) levels.[3,5] Glutathione, an antioxidant, is gaining traction as an oral option for melasma treatment. Oral and topical glutathione inhibits tyrosinase thereby skewing the production of eumelanin to pheomelanin.[6] In a study of 30 Filipino women, Handog et al. (2016) showed a moderate lightening in 90% of patients with 500mg glutathione buccal lozenge.[7]

Chemical peels are a form of topical treatment and should not be hastily discounted from the treatment of melasma. The idea behind a chemical peel is to cause controlled epidermal dyscohesion and regeneration. Chemical peels can assist in multiple areas of melasma treatment – removal of epidermal melanin and melanin in keratinocytes and stop transfer of melanosomes into keratinocytes.[8] Chemical peels are generally more useful for superficial melasma – higher concentrations and deeper peels carry the risk of PIH. Lactic acid has the best evidence supporting its use but improvements are seen with other peel regimens.

There are many different energy-based devices that have been studied in the treatment of melasma; intense pulsed light (IPL), Q-switched lasers (QSL), picosecond lasers (PSL) and fractionated and non-fractionated ablative and non-ablative lasers.[4] We agree that, whilst there are several studies looking at these modalities, they tend to have small population sizes, therefore it can be hard to draw inference from each individual study. However, when you begin to look at all the studies as a whole then there appears to be a significant

role that energy-based devices can play in the treatment of melasma.

We strongly encourage the use of skin priming topical and oral treatments before, during and after energy-based device use to limit the risk of PIH and the recurrence of melasma. This is supported by the literature.[8]

QSL selectively targets the chromophore melanin with pulse durations in the nanosecond range. This causes photoacoustic effects to result in melanin destruction.[4, 10] The Q-switched neodymium:yttrium-aluminium-garnet laser (QNd:YAG) operating at 1064 nm bypasses the epidermis. It is able to target dermal melasma which may be resistant to topical treatments.[4, 8, 10] Laser toning is the concept that using low-fluence, large spot size enables subcellular selective photothermolysis – destruction of melanin only without damage to the cell.[4, 8, 10, 11]

The fractionated non-ablative laser operating at both 1550 nm (erbium:glass) and 1927 nm (thulium fibre) has been shown to be effective for melasma. The erbium:glass 1550 nm is the only laser approved by the Federal Drug Administration in the United States of America for the treatment of melasma.[8] The erbium:glass 1550 nm laser has been shown to be as effective as 70% glycolic acid peels with an approximate 60% reduction in MASI score in one study whilst another showed it to be as effective as the traditional triple compound topical therapy approach suggesting it has a role when topical treatment is inappropriate or ineffective.[12, 13] The thulium fibre 1927 nm laser targets more superficially than the 1550 nm and has been shown to be effective for melasma when used with low energy and low density settings.[14,15] It is absorbed at the level of the dermo-epidermal junction where epidermal melasma is generally located and has been shown to reduce melasma by 50% in one study.[16]

IPL, a non-laser light source, emits broadbands of light of wavelengths between 515 to 1200 nm. It has the advantage of targeting epidermal and dermal pigment owing to the range of wavelengths produced, a rapid rate of thermal diffusion and large spot size.[16] Wang et al. (2004) showed an almost 40% improvement in objective melanin readings in the skin but these results were not maintained in the long term.[17] The therapeutic threshold with IPL is slim and in melasma should only be used by very skilled practitioners to reduce risk of PIH and rebound melasma.[8]

Fractionated ablative laser (CO_2 and Erbium:YAG) has long been considered inappropriate for use in melasma owing to the bulk dermal heating and significant PIH that can result.[8,16] However, a study comparing the use of low-fluence fractional CO_2 laser against low-fluence QNd:YAG in a split-face study design found that both lasers had a significant reduction in the modified Melasma Area and Severity Index (mMASI) compared to baseline and the CO_2 laser treated side had a statistically significant greater reduction that the QNd:YAG with neither side showing significant adverse effects.[18] We do not recommend ablative laser as a device of choice for treatment of melasma. However, we do successfully use ablative lasers, in patients with melasma who are seeking improvements for severe acne scarring or heavy rhytids and elastosis. In this group, patients are counselled of risks of rebound, thoroughly pre-treated, and closely followed up with photoprotection and tyrosinase inhibitors.

The latest generation of pigment lasers are the PSLs. Originally developed for tattoo removal, this group of lasers is useful in the treatment of multiple conditions, particularly in patients with skin of colour.[21] The PSL has a pulse duration in the picosecond range which provides an even greater photoacoustic effect than nanosecond lasers and potentially less risk of PIH.[21] In practice, however, this can be variable based on the wavelength used, actual pulse duration and importantly experience of the operator. The PSL also delivers higher, more targeted energy to melanin and therefore potentially offers greater clearance rates in stubborn melasma. A split-face study using fractional PSL found that, compared to the 4% hydroquinone alone side, PSL + 4% hydroquinone showed a statistically significant improvement in MASI scores.[21] There was no reported PIH.

Pulsed-dye lasers operating in the 585-595nm range have been shown to be effective in treating melasma in conjunction with the QSL compared to QSL alone, in patients who clinically demonstrate signs of vascular melasma.[8, 23] This ties in with the increasing understanding of the role that VEGF plays in the pathogenesis of melasma as discussed above.

Topical therapies are the gold standard for melasma treatment. However, combination treatments have the potential of providing more rapid clearance of melasma and may be integrated into a plan for long term maintenance.

We must consider all the options for melasma treatment; tailor the plan to suit our patient's individual melasma and needs – and consider energy-based devices as part of our regimen.

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Complications from Melasma Treatment

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Introduction

Melasma is an acquired hyperpigmentation disorder that appears as symmetric, brownish-grey macules and patches mainly on the face, and less commonly on neck, chest and forearm. Although asymptomatic, it can negatively impact the quality of life and self-esteem of affected individuals.

Increased understanding of the pathogenesis of melasma has led to the discovery of novel therapeutic targets. It is now recognised that melasma is a complex process involving the interaction between UV radiation, genetics, hormonal alteration, inflammation and vascular changes.[1] Hyperpigmentation results from increased synthesis of melanosomes in melanocytes and increased transfer of melanosomes to keratinocytes. Traditional treatments aim to inhibit these two processes. More recently, newer treatments are being considered to target the similar histological abnormalities between melasma and photoaging skin, including solar elastosis, mast cell and sebaceous gland proliferation, basement membrane alteration and increased vascularisation.[1]

The chronic and relapsing nature of melasma makes it difficult to find a treatment that can be used long-term without any adverse effects. The treatments available for melasma can be considered in four categories: topical, oral, laser and light-based, and chemical peels. In this article we will discuss the complications associated with each treatment modality.

Topical therapy

Sunscreen. Visible light and UV radiation can both induce hyperpigmentation and photoaging through similar mechanisms involving production of reactive oxygen species. Photoprotection is an essential part of any melasma treatment regimen. Sunscreen constituents are classified by mechanism of action as chemical (absorb UV rays) or physical blockers (scatter UV rays). In melasma, sunscreen combining iron oxide (a physical blocker) and broad spectrum UV filters are superior to UV-only sunscreen, due to protection from shorter wavelengths of visible light.[2, 3] Zinc oxide and titanium dioxide are other common physical blockers in use; both are photostable and there are no reports of adverse skin reactions. The main adverse reaction from sunscreen is skin irritation, which ranges from hypersensitivity reaction to contact dermatitis. Irritant contact dermatitis is more common than allergic contact dermatitis.[4] Although more than 120 chemicals act as UV filters, it is mainly inactive chemicals that are responsible for adverse reactions from sunscreen.[4, 5] These include preservatives, fragrance materials and emollients in various forms of sunscreen products. Adverse reactions have become less common since the removal of many of the implicated compounds. Of the UV filters, benzophenones and dibenzoylmethanes are the most common cause of allergic contact dermatitis.[4, 5] Concerns about carcinogenic and endocrine effects from systemic absorption of oxybenzone have not been substantiated.[6] Avobenzone, the most widely used UVA filter in sunscreen, is degraded by UV radiation and needs to be photostabilised by addition of an antioxidant. Avobenzone breakdown products and avobenzone stabilisers have the potential for inducing a photosensitivity reaction.[7] Patch testing to photosensitising chemicals is advised for individuals with a history of photodermatosis in order to guide choice of sunscreen.

Hydroquinone. Hydroquinone (HQ) is the most well-studied topical agent and remains the first-line treatment for melasma. A tyrosinase inhibitor, HQ prevents the conversion of DOPA to melanin. Adverse effects from HQ are related to treatment dose and duration. It is commonly used in preparations at 2 to 5% concentration applied once or twice daily. The depigmenting effect may take 5-7 weeks to occur, and treatment duration is usually for 3 to 12 months.[8] To improve efficacy, it is often used in combination

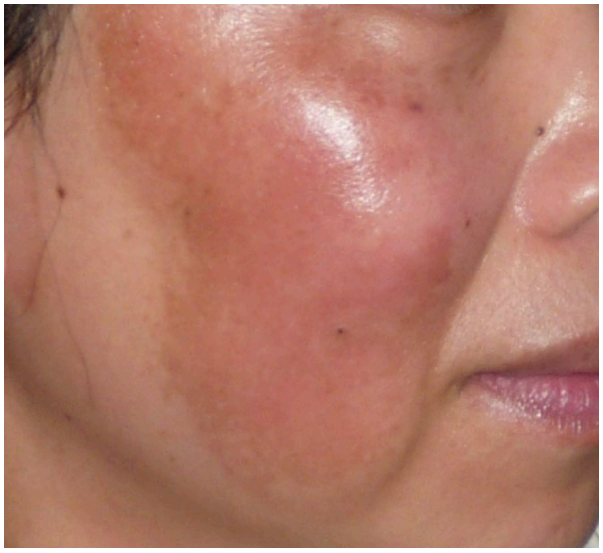

Figure 1. *Contact dermatitis from triple combination cream*

with topical retinoid and corticosteroid (see *Triple combination cream*), which also increases the risk of adverse reactions. The most common side effect is irritation.[8] Other side effects include erythema, burning, colloid milium, irritant and allergic contact dermatitis (figure 1), nail discoloration, transient hypochromia and paradoxical postinflammatory hypermelanosis.[8, 9] Prolonged use of HQ is associated with guttate hypomelanosis, whereby mottled depigmented spots appear on macules of melasma; and exogenous ochronosis, a blue-black hyperpigmentation of treatment areas.[9] For this reason, there is controversy regarding the safety of HQ in several regions, including Japan, Europe and USA, and some countries prohibit its use in cosmetic preparations.[9] Use during pregnancy should be avoided since 35-45% is systemically absorbed with the potential for adverse effects on the fetus, although to date none have been reported.[10]

Triple combination cream. The triple combination cream (TCC) of HQ, retinoid and corticosteroid is more effective than HQ alone for treating melasma but with increased risk of adverse reactions. The original Kligman's formula introduced in 1975 consists of HQ 5%, tretinoin 0.1% and dexamethasone 0.1%.[11] Newer formulations have been developed to reduce irritation while improving efficacy. Currently, HQ 4%, tretinoin 0.05% and fluocinolone acetonide 0.01% is favoured. Erythema, desquamation, burning, dryness and pruritus can occur due to the retinoid.[8] Steroid-induced atrophy and telangiectasia has also been reported in several studies, where TCC was used for at least 8 weeks, although they were uncommon.[12, 13] Generally, side effects were mild and transient, with very few patients discontinuing treatment.[13] TCC is regarded as a safe and effective long-term treatment.

Other tyrosinase inhibitors. *Azelaic acid* (AA) reduces PUVA-induced senescence in fibroblasts; additionally, it reduces fibroblast secretion of growth factors that promote melanogenesis and melanocyte proliferation.[14] AA may also be involved in mediating inflammation. In clinical trials, 20% AA had similar efficacy to 4% HQ but an increased risk of irritation.[8] *Rucinol* serum also showed improvement in melanin index in studies but was associated with stinging, burning, pruritus.[8]

Retinoids. Retinoids have multiple effects on melanin production and expression, including inhibiting tyrosinase transcription, increasing keratinocyte turnover, inhibiting melanosome transfer and facilitating trans-epidermal penetration of other topical agents.[8] Pigment reduction is observed, but in studies it was used at high concentration (0.1% tretinoin cream) for a long duration (can take 24 weeks to see effect)[15, 16] and has a high rate of side effects including burning, irritation, pruritus, desquamation and erythema.[8] At a lower concentration of 0.05%, tretinoin twice daily had no significant improvement compared to vehicle and sunscreen.[8] Adapalene 0.1% gel has similar efficacy but less side effects compared to 0.05% tretinoin cream.[8]

Cysteamine. Cysteamine is an endogenous intracellular antioxidant that is produced by conversion of coenzyme A to pantethine and then to cysteamine.[17] It has several biological uses, notably a depigmenting effect on in vitro melanocytes. Compared to HQ, tachyphylaxis and ochronosis have not been reported with long-term use of cysteamine and it has good potential in recalcitrant melasma. Clinical trials have shown efficacy and safety for treatment of melasma.[18, 19] Apart from transient erythema after the first application, there was no significant difference with placebo for dryness, itching, burning and irritation. In one study, cysteamine improved melasma in a patient refractory to TCC (5% HQ, 1% dexamethasone, 0.05% retinoic acid) over a 3-year period.[20] The burning sensation, telangiectasia and erythema from TCC significantly improved after cysteamine was started, and no side effects were reported with maintenance use. On 3-year follow up no skin atrophy was noted.

Kojic acid. A tyrosinase inhibitor and ROS scavenger, kojic acid is more effective as an adjunct to other topicals than as monotherapy, but is more irritating and expensive than HQ.[21] Burning and irritant contact dermatitis are also reported. In one trial, 2% kojic acid combined with 10% glycolic acid and 2% HQ gel showed better pigment scores versus glycolic acid and HQ gel alone. However, transient erythema, stinging and exfoliation was observed in all cases.

Ascorbic acid or vitamin C, also binds with copper of tyrosinase to inhibit tyrosinase activity and suppress melanin synthesis.[1] Although 5% ascorbic acid was shown to be inferior to 4% HQ in improving melasma,

it was associated with less skin irritation (6% vs 69% for HQ).[22] Topical ascorbic acid has very minimal side effects and is considered a safe and effective therapy used alone or in combination.[23] 5% AA combined with 20% trichloroacetic acid (TCA) peel was better than TCA alone in improving and maintaining clinical improvement.[24]

Other natural ingredients. Natural ingredients applied topically are being explored in the treatment of melasma due to their antioxidant and anti-inflammatory properties. These include liquorice, orchid, green tea, turmeric, arbutin, coffeeberry, and mulberry extracts.[25] Some ingredients such as niacinamide, liquirtin and soybean are also reported to disrupt melanosome transfer by inhibiting keratinocyte protease-activated receptor-2 (PAR-2).[25] There are limited studies with mixed results. Long-term side effects are unknown as studies evaluating these ingredients were of short duration.[26]

Summary: Sunscreen constituents may cause irritant or allergic contact dermatitis. HQ is the most widely used treatment for melasma, with well-known adverse reactions ranging from acute irritation and contact dermatitis, to guttate hypomelanosis and exogenous ochronosis with chronic use. It is recommended to use rotational therapy, or a lower concentration in a topical combination, to reduce risk of ochronosis and tachyphylaxis. TCC is an efficacious long-term treatment for melasma but there are adverse reactions from the retinoid and corticosteroid component. Non-HQ tyrosinase inhibitors have a lower incidence of contact dermatitis, as well as tachyphylaxis/ochronosis. Cysteamine shows promise as a safe and effective alternative to HQ. Natural ingredients including kojic acid, ascorbic acid and others are useful and safe as adjuncts.

Oral therapy

Tranexamic acid. Tranexamic acid (TXA) is traditionally used as an anti-fibrinolytic haemostatic agent. It inhibits plasmin, which converts extracellular matrix-bound VEGF into its free forms.[1] TXA also suppresses neovascularisation-induced bFGF. As a result, TXA may reverse the dermal vascular changes in melasma. Furthermore, it may inhibit melanin synthesis by blocking the interaction between melanocytes and keratinocytes.[27] The first published use of TXA for melasma was in 1979. It is used in oral, topical and injectable forms. Oral dosage ranges between 500 to 1,500 mg/day. A meta-analysis reports TXA improves melasma either alone or as adjuvant therapy.[27] Pooled data from TXA-only observational studies showed a significant decrease in melasma area and severity index (MASI) of 1.60 post-TXA treatment.[27] Several authors recommend TXA as first or second-line treatment for melasma, in combination with topicals.[8, 11] Greatest improvement is seen with oral, followed by microinjection and then topical TXA.[27] Decrease in MASI can take 3 months; however, there is a high relapse rate after treatment cessation (72% after 2 months in one study[28]) In melasma studies, main side effects of oral TXA included heartburn, nausea, abdominal cramps, epigastric discomfort; less common side effects were oligomenorrhoea, headache, myalgia, palpitations, urticarial rash with angioedema, numbness or facial pruritus, tinnitus, transient amnesia, tremor, hair shedding, facial hypertrichosis, lip and periorbital swelling, anxiety and depression.[29, 30] As a haemostatic, one should be cautious regarding the potential for deep vein thrombosis, pulmonary embolism, stroke and acute myocardial infarction. Thromboembolic events are rare at the doses used to treat melasma, which is usually ranges from 500 to 700mg daily[30], much lower than its use as a haemostatic agent.[27] Despite this, one case report of DVT occurred in an individual treated for melasma, who was later found to have familial protein S deficiency.[31] Therefore, clinicians should consider patient factors which may increase the risk of thrombosis, such as concomitant oestrogen, pregnancy, coagulopathy, epilepsy and severe renal impairment.[29] Topical and injectable TXA is not known to cause systemic side effects, but local erythema, irritation, xerosis and scaling have been reported.[32] Two cases of hypopigmentation have been reported with monthly intradermal TXA injection, which appeared as early as 4 months post-treatment initiation.[33]

Summary: TXA is an effective, off-licence, therapy which should be considered second-line treatment for melasma. Careful patient selection is important, and clinicians should consider the risk of thromboembolic disease before commencement. Frequent TXA injections may rarely lead to hypopigmentation, and treatment sessions should be limited.

Laser and energy-based therapy

Intense pulsed light. Results of IPL on melasma improvement have been mixed, some studies showing superior results with IPL combined with HQ, TCC and TXA compared to IPL alone.[8, 34] Recently, fractionated IPL has demonstrated superior efficacy for hyperpigmentation than conventional IPL. In contrast to laser, IPL generates wavelengths (515-1200 nm) that simultaneously target epidermal, dermal and vascular abnormalities involved in melasma. Adverse effects include erythema and tingling, skin exfoliation, post-inflammatory hyperpigmentation, proportional to the energy intensity.[34] In one study, 24% of subjects who improved with IPL developed recurrent pigmentation within 24 weeks.[35] Overall, improvement with IPL is modest and is best suited to skin types I-III.[11] It is recommended to use low-fluence or fractionated IPL to minimise the risk of PIH.[11] In darker skin types, a

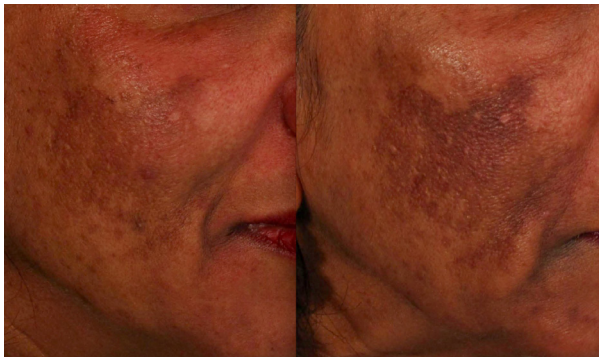

Figure 2. *PIH complicating melasma therapy with 1927nm fractional laser*

1-2 week recovery time can be expected.[36] To reduce recurrence, topical therapy should be continued at least 6-12 months post-treatment.[37]

Non-ablative fractionated laser (NAFL). Non-ablative lasers should be used over ablative lasers for melasma as they cause less inflammation and hence lower risk of PIH. NAFL targets water-containing tissue and creates columns of microthermal damage within the dermis, stimulating dermal collagen remodelling and removing dermal melanophages. Erythema, crusting and oedema are common post-treatment, usually resolving within 7 days. The 1550/1540 nm NAFL was approved by the United States FDA in 2005 for treatment of melasma. Studies show good results but erythema, swelling and pain occurred frequently and there was a high incidence of PIH and rebound pigmentation.[37] It is effective in clearing melasma used alone or combined with TCC (>50% patients had >75% clearance after 3 months) but clearance rates decreased to 21-52% at 6 months, suggesting a high recurrence rate.[38-40] Overall, 1550nm NAFL appears comparable in efficacy to TCC, but relapse occurs within a few months and there is a high incidence of adverse effects. It is recommended to use lower fluences, variable pulses and pretreatment with HQ to minimise complications.[36] The 1927-nm NAFL shows promise for refractory melasma. Improvement appears to be sustained longer than other lasers. Despite the small study size, one study showed 60% patients having >50% clearance of melasma 1 month following a single treatment, and 53.8% at 6-12 months post-treatment.[41] Recurrence was reported by 46% of patients at mean 10.2 months post-treatment. Unlike IPL and Q-switch lasers, which should only be considered for skin types I-III, the 1927-nm NAFL can be used for skin types III to VI.[37] Nevertheless, PIH is also possible with this modality (Figure 2).

Q-switch laser. When used as monotherapy, the Q-switch lasers which target melanin – ruby (694nm), alexandrite (755nm) and neodymium:yttrium-aluminioum-garnet (532 nm or 1064nm) lasers did not demonstrate any long-term benefit in melasma.[37, 42] They are each associated with high incidence of PIH and rebound hyperpigmentation. Low-fluence Q-switch laser protocols were introduced to overcome this drawback, with 1064 nm QS-Nd:YAG laser currently the most popular in use.

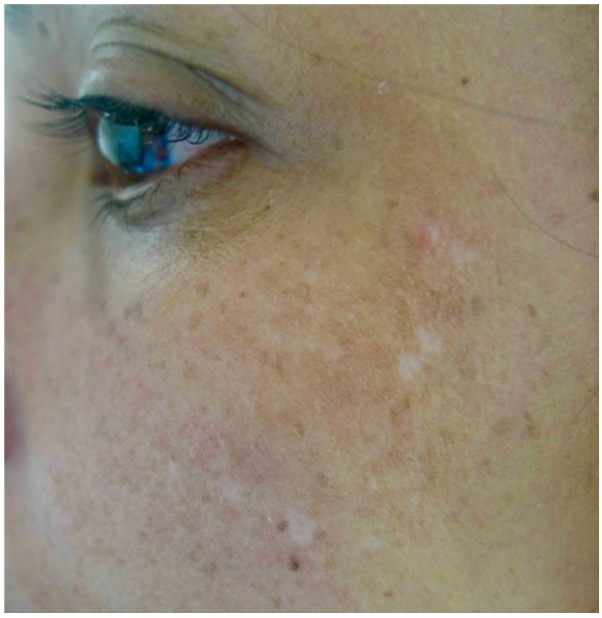

Figure 3. *Mottled hypopigmentation after multiple sessions of QS-Nd:YAG therapy*

1064 nm QS-Nd:YAG laser (QSNYL). Separate studies showed that it was more effective combined with 2% HQ, TCC, glycolic acid peel, microneedling and topical TXA. Mottled hypopigmentation is a known adverse effect, occurring more frequently with high-fluence laser. The "laser-toning" technique using a low-fluence 1064-nm QSNYL is one of the first-line therapies for melasma in East Asia.[1] It is postulated to work by using high-peak power of ultrashort pulse duration (5ns) to selectively destroy melanosomes and dendrites of melanocytes without damaging the melanocyte itself, a process termed 'subcellular-selective photothermolysis'.[36, 43] This was reported to be clinically beneficial with lower risk of PIH. However, repeated laser-toning may lead to mottled hypopigmentation[44] (figure 3), and recurrence rate is high as this technique does not penetrate into the dermis.[1] Two studies reported a 3-month post-treatment recurrence rate of 64% and 81% respectively.[45, 46] Another disadvantage from these studies is that a high number of treatments are required over short treatment intervals (weekly) compared to other lasers.[37] We recommend treatment intervals of at least 2 weeks and limiting treatments to 10 sessions, to reduce the risk of hypopigmentation. Topicals such as TCC should be applied post-treatment to reduce recurrence.

Picosecond laser. As the name implies, these lasers apply a picosecond duration of wavelength energy to skin, which may induce pigment displacement without the

Figure 4. *PIH complicating melasma therapy with picosecond laser*

secondary thermal damage associated with other lasers. Recent studies show promising results of picosecond combined with HQ, with few adverse effects.[47-50] These include mild transient erythema and desquamation. However, these studies are of short duration only and more data is required. PIH has been observed with picosecond laser treatment of melasma (figure 4).

Pulse dye laser (PDL). PDL is thought to work by targeting the vascular changes in melasma. PDL combined with TCC has shown better results than TCC alone.[51] However, benefit was not observed in darker skin and it caused significant PIH, so its use should be reserved for skin types I to III.

CO2 fractional and ablative lasers. These have a high risk of side effects including PIH and dyspigmentation (due to causing cell destruction and thermal injury), and few long-term trials have been conducted. CO2 lasers penetrate to a depth dependent on the skin water content and are non-selective for melanin. They are currently not recommended as treatment for melasma. Low-fluence CO2 fractional laser has been reported to have higher efficacy compared to 1064nm QSNYL with no difference in adverse effects, but the study period was only 2 months.[52]

Microneedling. Microneedling is conventionally used to improve skin tone and texture by utilising micron-length needles to create pores in the skin and subsequently induce elastin and collagen remodelling. It is also used to facilitate delivery of topical agents. Recent applications in melasma show benefit, but studies were of low quality and did not evaluate it as monotherapy; in one small study no relapse was reported in microneedling and TCC therapy after 6 months.[53] Erythema, pain and discomfort are generally well-tolerated, and the risk PIH was very low.[54]

Summary: laser and energy-based therapies are commonly used in the treatment of pigmentary disorders including melasma. It is important to note that the improvements are not permanent and there is a high risk of adverse effects. It should be considered third-line treatment for melasma and used in combination with topicals. All treatments can cause PIH and burns. Therefore, patient selection is essential, particularly for darker skin phenotypes, as some can worsen hyperpigmentation. Another caveat is that approximately 50% of patients will have recurrence within 3-6 months of laser or light treatment regardless of device used.[11] The longest delay to recurrence is with NAFL, then IPL, then Q-switch.[11] Traditionally, lasers aimed to cause destruction and death of pigment-containing cells, which triggered an inflammatory response that leads to PIH, mottled hypopigmentation, and recurrence of pigmentation on sun exposure. Laser treatment now focuses on the principle of subcellular selective photothermolysis, using high-peak power of ultrashort duration to reduce heating and inflammation, and subsequently lower the risk of adverse effects. In this sense, 1927nm NAFL[36] and 1064 nm QSNYL[36] is recommended for darker skin types, and IPL /PDL for lighter skin types. If Q-switch laser is used, low fluence and treatment intervals at least 2 weeks will minimise the risk of post inflammatory hypopigmentation. Despite FDA approval and effectiveness for melasma, nonablative fractionated 1550 nm laser has a high rate of complications and is not superior to TCC. CO2 lasers are generally not recommended for melasma. There is promise for picosecond lasers but more studies are required.

Chemical peels

Trichloroacetic acid (TCA). Traditionally, TCA is used at 35% concentration as a photoaging treatment, but this commonly caused rebound hyperpigmentation. Lower concentrations are used in melasma to avoid this complication. TCA and medium depth peels have been used to treat melasma with relatively high clearance rates when combined with topicals. One study showed 87% clearance at 4 months with 20% TCA and topical ascorbic acid[24], 80% clearance at 6 weeks of 20% TCA and magnesium ascorbyl phosphate cream[55], and 71% at 8 weeks of 15% TCA and Jessner's solution, which is also reported to reduce the risk of PIH.[56] PIH occurred in 10% patients treated with TCA alone. 10-20% TCA peels have similar efficacy to GA peels but higher incidence of burning and peeling.[57, 58]

Glycolic acid (GA). In melasma studies no significant difference was observed between GA and HQ, when GA is used alone or in combination, but GA combined with other topical agents (TCC, AA) show benefit.[59-62] Importantly, however, all treatment regimens which included GA were associated with PIH.

Salicyclic acid (SA). SA peels have not shown any significant melasma improvement as monotherapy versus Jessner's solution, or combined with HQ or vitamin C.[63-65] Combined SA and mandelic acid peels showed equal efficacy but was better tolerated compared to GA in an Indian population.[66] Side effects were generally mild and transient, including burning and irritation.

Novel peels. Other peels include retinoic acid (tretinoin) and lactic acid peels. Tretinoin peel at 1-10% concentration were effective in reducing MASI, with less irritation compared to 70% GA.[67, 68] 82% lactic acid has also shown efficacy with burning as the only side effect, which was well tolerated [69]. However, studies were small and of short duration. Thus, larger controlled trials are necessary regarding optimal concentration and dosing of these agents.

Summary: Peels are commonly used for skin rejuvenation and dyspigmentation. In a few studies to date, they have not been shown to be superior to topical therapy alone for melasma. Compared to topicals, peels have increased acute side effects including burning and discomfort, and PIH in the longer term.[8] 10-20% TCA and 1% tretinoin are similar to GA for efficacy but TCA is more irritating, whereas tretinoin is less irritating. SA/mandelic acid peel may be better tolerated in darker skin types.

Conclusion

Melasma is a complex disorder with genetic, hormonal, inflammatory and environmental factors contributing to hyperpigmentation. As knowledge of its pathophysiology has evolved, new therapeutic targets have emerged to complement established treatments. The current challenge is that no single treatment produces long lasting results and all have adverse reactions (table 1), depending on the modality, intensity and frequency of application. Irritation and dryness are common with topical agents; serious reactions are steroid-induced atrophy, ochronosis with HQ and contact dermatitis with HQ and sunscreen allergens. Oral tranexamic acid is beneficial if there are no contraindications to cardiovascular and thromboembolic disease. Laser and energy-based devices have a risk of inducing PIH and burns; they should be used after topicals are trialled, and in combination with topicals such as HQ or TCC. Chemical peels are associated with skin irritation and PIH and should not be used alone for melasma. Cysteamine and picosecond lasers show promising results in limited studies. Large controlled trials are needed to evaluate the safety and efficacy of these novel treatments before they can be recommended in clinical practice.

Table 1. *Summary of adverse reactions and precautions to melasma treatments*

Treatment	Common side effects	Rare side effects	Precautions
Topicals			
Sunscreen	Irritation	Contact dermatitis – allergic/irritant	Allergy to sunscreen ingredients
Tyrosinase inhibitors	Irritation, burning, erythema	Contact dermatitis – allergic/irritant, transient hypochromia, colloid milium, nail discolouration, paradoxical postinflammatory hypermelanosis, guttate hypomelanosis, exogenous ochronosis	Tachyphylaxis, exogenous ochronosis with chronic use; hydroquinone is contraindicated in pregnancy
Retinoids	Irritation, burning, pruritus, erythema	Desquamation	
Corticosteroids	Irritation, peri-orofacial dermatitis, steroid rosacea	Skin atrophy, telangiectasia, easy bruising	
Cysteamine	Erythema, dryness, itching, burning, irritation		
Natural ingredients	Irritation		Lack of data about long term safety
Tranexamic acid	Erythema, irritation, xerosis, scaling Injection site pain and oedema with intradermal tranexamic acid		
Orals			
Tranexamic acid	Heartburn, nausea, abdominal cramps, epigastric discomforts	Oligomenorrhoea, headache, myalgia, palpitations, urticaria and angioedema, numbness, facial pruritus, tinnitus, tremor, transient amnesia, tremor, hair shedding, facial hypertrichosis, lip and periorbital swelling, anxiety and depression	Contraindicated in pregnancy and risk factors for cardiovascular or thromboembolic disease
Laser and energy devices			
IPL **NAFL** **Qswitch** **Picosecond** **CO2 laser** **Microneedling**	Erythema, irritation, pain, swelling, desquamation, exfoliation, PIH Mottled hypopigmentation (Qswitch)	Thermal burn	IPL: not suitable for darker skin types 1927nm NAFL and Qswitch lasers: suitable for darker skin types CO2 lasers: generally not recommended for melasma
Chemical peels			
Trichloroacetic acid **Glycolic acid** **Salicylic acid** **Mandelic acid** **Tretinoin** **Lactic acid**	Burning, irritation, PIH	Rebound hyperpigmentation (with higher concentration of TCA)	SA/mandelic acid peel better tolerated in darker skin types

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Melasma – What's on the Horizon?

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Sarkar R, Nayak, P. Melasma – What's on the Horizon? Opin Prog Cosmet Dermatol 2020;1(1):47-48.

Melasma—a chronic acquired localised hypermelanosis— is difficult to treat and common in adult females. There are many treatment modalities available for treatment of melasma, such as depigmenting agents, chemical peels, laser, and light therapy.[1]

The identification that all melasma is "mixed" has suggested various potential targets for its treatment. Several levels are being targeted by novel agents, from classically targeting the melanogenesis pathway, to acting on hyperactive melanocytes, reducing free radical production, and inhibiting melanosomal transfer to keratinocytes. Few newer drugs may act by restoring the hormonal levels or skin barrier, while others target the mast cells and dermal vessels.[2]

A. Conventional

Conventional skin-lightening agents such as hydroquinone and azelaic acid exert their effects selectively in hyperactive melanocytes. Most conventional whitening agents inhibit melanogenesis and its regulation.[2,3,4]

B. Novel

Include the following based on the pathogenesis targeted:

1. Hyperactive melanocytes

Inhibiting the activity of melanocytes in addition to reducing melanin synthesis is more effective in improving melasma.

Include ascorbic acid, glutathione, arbutin, linoleic acid, rucinol, gentisic acid, hydroxycoumarins, alpha lipoic acid, mequinol, dimethyl hydroxy furanone, aloesin, flavonoids, green tea, liquorice derivatives, magnolignan, antisense oligonucleotides, N-acetyl-4-S-cysteaminylphenol, epigallocatechin, ellagic acid, cinnamic acid – which are involved in specifically targeting hyperactive melanocytes and the genes (tyrosinase, TYRP1, TYRP2, and MITF) involved in melanogenesis.[2,3] GSH decreases tyrosinase and skews conversion of eumelanin to pheomelanin.[3] Methimazole can be used topically as it is a peroxidase inhibitor and blocks melanin synthesis.[3]

2. Melanosomal transfer

Drugs inhibiting the keratinocyte protease-activated receptor 2 (PAR-2) inhibit melanosomal transfer and have been shown to be effective in melasma.

Include niacinamide, liquirtin, soymilk/soybean trypsin inhibitor, and lectins which block the entry of melanosome from melanocytes to keratinocytes.[2]

3. Oxidative stress

These molecules reduce the inflammation and decreases ROS production.

Include liquorice extract, oral proanthocyanidin, Vitamin A, E, C, niacin, glutathione, N-nicotinoyl dopamine, pycnogenol, polyphenols, epigallocatechin-3-gallate, mulberry extract, orchid extract, coffeeberry extract, acidified amino acid peels – these have antioxidant and anti-inflammatory activity. Melatonin is a potent antioxidant/free radical scavenger.[2,3]

4. Vascular component

Tranexamic acid (TXA) inhibits the plasmin/plasminogen pathway. This results mainly in interference of keratinocyte and melanocyte interactions thus inhibiting melanin synthesis.[2,4]

5. Oestrogen

Oestrogens upregulate the synthesis of enzymes that are involved in the production of melanin, including tyrosinase, TRP-1, TRP-2, and MITF. Oestrogens also upregulate estrogen receptors in the lesional skin. There are suggestions that a "triple therapy of the future" could include a hydroquinone, an antiestrogen, and a vascular endothelial growth factor (VEGF)

inhibitor.[2,4] Flutamide is an antiandrogenic agent can be used topically in melasma.[3]

6. Histamine and mast cells

There is an increase in histamine and mast cells in melasma, in turn stimulating the proliferation of melanocyte through H2 receptors. Mast cells can also promote vascular proliferation by producing VEGF, transforming growth factor- beta and fibroblast growth factor-2. Oral tranexamic acid and zinc are known to reduce activity of mast cells.[2,4]

7. Others

Curcumin by its antiinflammatory, free radical scavenging, UVprotective activities may serve as a novel skinlightening agent of the future, both as a topical and an oral preparation.[2] Lignin peroxidase is another potential future therapy, as lignin is structurally similar to melanin, and lignindegrading enzymes can be utilised to decolorise melanin.[2] In platelet rich plasma, TGF-β1 released from α-granules in platelets has been shown to cause significant inhibition of melanin synthesis through delayed extracellular signal-regulated kinase activation.[2,5]

Microneedling has been used to enhance drug delivery.[2,6,7] A number of new peeling agents are being developed for the treatment of melasma including tretinoin peel, Obagi blue peel (fixed concentration trichloroacetic acid with a blue peel base), and amino acid fruit peels.[7]

Lasers and energy-based devices have seen a surge in recent times in the treatment of melasma. Laser treatment is discussed in detail in various articles in this issue.

Conclusion

Melasma treatment is vast but not yet complete. Treatment of melasma has taken centre stage over the past 2-3 decades in dermatology. In the foregoing research and advances in dermatology, newer aspects in pathogenesis and treatment of melasma has surfaced every now and then, but the efficacy of these modalities are yet to be ascertained.

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Melanin Hyperpigmentations: Effective and Lasting Treatment of Melasma in Patients with a Multi-ethnic Profile using dermamelan®

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Introduction

Melasma is a type of hyperpigmentation characterised by the appearance of **generally symmetrical pigmented stains** on the face, particularly on the cheeks, dorsal surface of the nose, forehead and upper lip.[1,2,3] It is **common in women of all ethnic groups and skin phototypes**, but it is most frequent in Asian, African and Latin American individuals.[4]

Numerous treatment options have been consolidated in the last decades. In this regard, a distinction can be made between treatments that seek to eliminate the melanin deposits and those that seek to regulate melanin synthesis within the melanocyte.

In relation to the elimination of melanin, laser therapy and intense pulsed light (IPL) are popular and widely used solutions, but they are expensive and invasive, have demonstrated heterogeneous efficacy in multi-ethnic profiles and even pose a high risk of post-inflammatory hyperpigmentation.[5]

Furthermore, there are many topical treatment alternatives: chemical peelings, creams containing acids to accelerate epidermal turnover, and even medical topical formulations based on hydroquinone, to regulate melanocyte activity.

All these therapies represent a partial solution to a very complex problem that **requires a multi-focal approach capable of securing melanin elimination and regulation with the purpose of affording a short and long term solution, with maximum patient safety regardless of ethnic group or phototype**.

Objective

To evaluate the efficacy and safety of the **dermamelan®** method in treating facial melasma among patients with a multi-ethnic profile and differentiated skin phototypes (according to the Fitzpatrick scale).

dermamelan® offers a multi-focal approach to melasma treatment and control, thanks to its corrective and regulatory effects that modulates melanin synthesis, reduces transfer of the pigment from the melanosomes to the keratinocytes, while also eliminates melanin accumulation at epidermal level.

Methods

A retrospective analysis was made of 33 cases of mixed melasma corresponding to Caucasian, Asian, African and Latin American ethnic groups with skin phototypes II-V, treated with the **dermamelan®** method between October 2013 and May 2016.

The treatment protocol comprised a clinic session for renewal of the dermis and reversible inhibition of melanogenesis, combined with home treatment to complete epidermal turnover and regulate melanogenesis.

Step 1: AT THE CLINIC

Application of the full 10 grams of dermamelan mask as a thick layer on the entire face, with increased thickness over the hyperpigmentation zones. The product was allowed to act upon the skin for the recommended time according to the skin phototype involved:*

- **Phototypes I and II:** 8 hours
- **Phototypes III and IV:** 10 hours
- **Phototypes V and VI:** 12 hours

** The product application times can be modulated according to medical criterion and considering the individual characteristics of the patient and skin ethnic group. In Asian patients with a thinner skin horny layer may experience increased sensitivity and it is advisable to limit the application time to a maximum of 8 hours.[4,6]*

Step 2: AT HOME

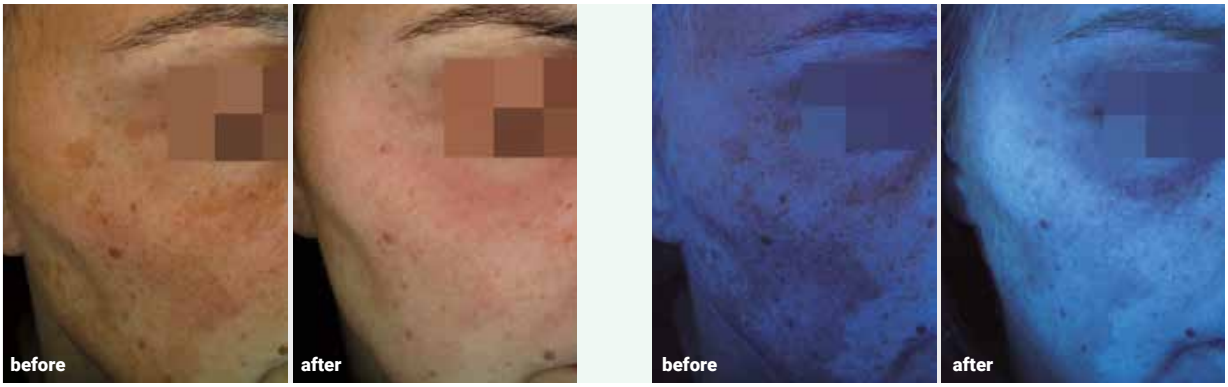
Application of the **dermamelan® treatment** maintenance cream, based on the following scheme:

Simultaneous hydration and solar protection is essential, applying melan recovery and mesoprotech melan 130+ pigment control.

Results

Clinical Evidence

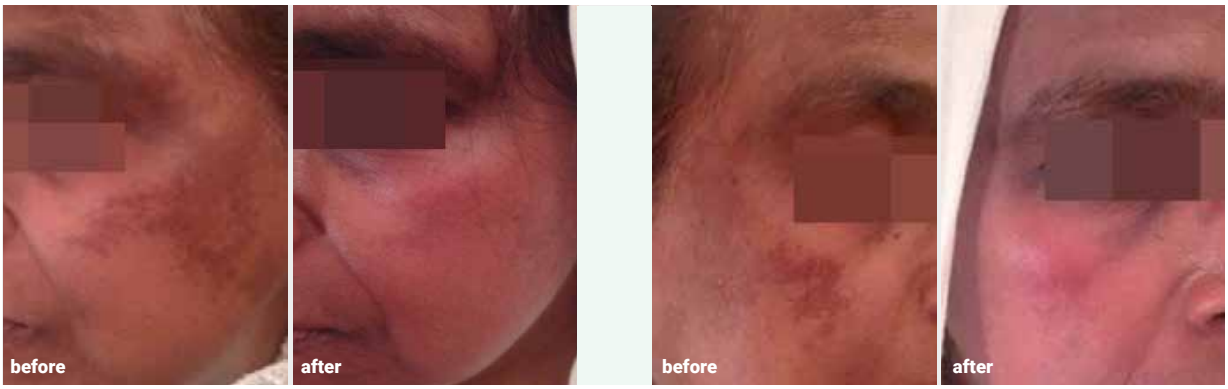
Age: 52 **PHOTOTYPE III** **MASI:** pre: 23.1 post: 9.9 Δ: **-57%**



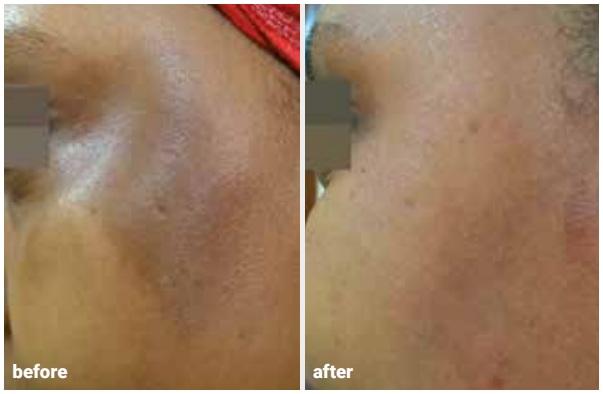
Age: 41 **PHOTOTYPE IV** **MASI:** pre: 27.3 post: 7.8 Δ: **-71%**

Images courtesy of Dr Pulvirenti

Age: 52 **PHOTOTYPE V** **MASI:** pre: 23.1 post: 9.9 Δ: **-57%**

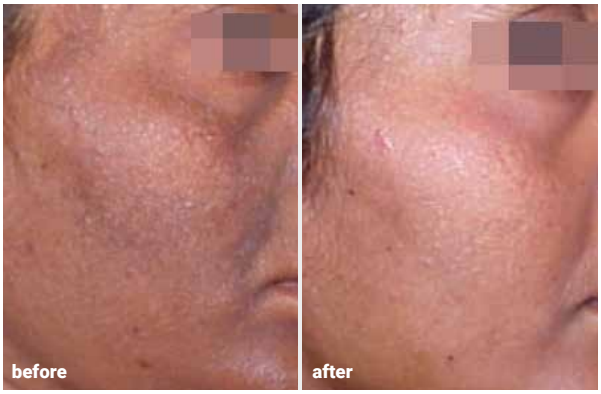


Age: 35 **PHOTO.V-MASI:** pre: 12.6 post: 4.8 Δ: **-62%**



Images courtesy of Dr Danmallam

Age: 41 **PHOTO.V-MASI:** pre: 25.5 post: 3.6 Δ: **-86%**



Images courtesy of Dr Reddy

In Vitro

Studies in human melanocytes have evaluated the melanin synthesis reducing capacity of the complex of ingredients contained in **dermamelan®** after 48 hours:[7]

control culture

48 hours culture with dermamelan active ingredients

Figure 1: *In vitro study. Melanin synthesis. Fontana-Masson stain. mesoestetic Pharma Group, S.L. 2014.*

In Vivo

The evolution of the hyperpigmentations was monitored up until day 120 of the study.

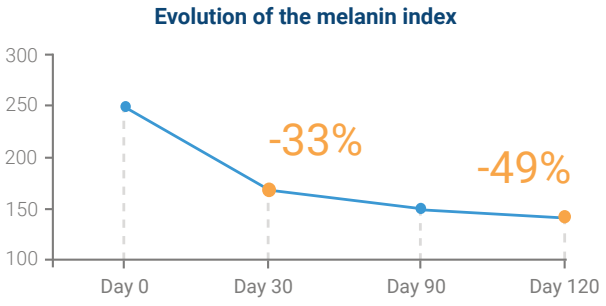


Figure 2: *In vivo study: Reduction of pigmentation as measured by evolution of the melanin index at each control point, calculated with the mexameter®.[8] mesoestetic Pharma Group, S.L. 2016.*

**Measurement made with the mexameter® (day 0, day 15, day 30, day 60 and day 120) and/or MASI[9] (before and after treatment)*

Conclusions

- Efficacy in 100% of the treated cases.*
- Visible results from the first week of treatment.
- Notorious improvement of skin quality and reduction of superficial wrinkles in 100% of the cases.
- No post-inflammatory hyperpigmentations were reported during the treatment.
- The **dermamelan®** method has been shown to be effective and safe in patients of all skin ethnic groups and phototypes.

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7. Biotechnology Unit. Study of melanin synthesis for dermamelan. mesoestetic Pharma Group S.L. 2014.
8. mexameter® (MX18-Courage Khazaka Electronic) system for objective measurement of the skin melanin index. Evaluation in a subgroup of 12 subjects.
9. Melasma Area Severity Index (MASI): subjective index quantitatively measuring the severity of facial melasma based on area, intensity and homogeneity.

dermamelan®

- **LEADER IN DEPIGMENTATION**
  Its trajectory, distribution, international presence and leadership support the credibility of the method.

- **UNIQUE, DUAL-ACTION SOLUTION**
  dermamelan has a dual effect, corrective and regulator, achieving short and long-term results by keeping pigmentation under control and preventing any recurrence.

- **PROVEN RESULTS**
  Empirical evidence shows the high degree of efficiency of the method. More than 100 clinical cases evaluated under medical control guarantee its short, medium and long-term efficacy.

- **HIGH DERMAL SECURITY**
  Strict quality standards and numerous *in vivo* studies demonstrate its excellent safety profile and skin tolerance.

- **HIGH PROFESSIONAL REPUTATION**
  Thousands of professionals around the world already treat pigmentation with the dermamelan method.

- **CUSTOMER SATISFACTION**
  Visible results from the first week of treatment and a long-lasting effect mean high satisfaction, well-being and enhanced patient quality of life.

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Assessment of Clinical and Dermatological Tolerance, of the Depigmenting Potential and of Cosmetic Properties of Mela Cream After 28 Days of Application

INVESTIGATED PRODUCT: Mela Cream

SPONSOR: DERMOSCIENCES Ltd

PURPOSE OF THE STUDY: Evaluate depigmenting potential by Mexameter® measurements, subjective effectiveness, clinical and dermatological tolerance and cosmetic properties of a cosmetic product after a 28-day application period.

INVESTIGATOR: Axelle CHENUT

CO-INVESTIGATOR: Doctor Dominique LARRUE, Dermatologist

SITE OF THE INVESTIGATION: 5 sites in Europe and 2 in Asia, certified ISO 9001: 2005 and GCP (Good Clinic Practice).

PERIOD OF INVESTIGATION: 12/03/2019 to 09/04/2019 in Bordeaux, France

Methodology

On D1, the investigator or the clinical assistant under the responsibility of the investigator examined the face of each volunteer. Each volunteer received the product to be tested as well the sun cream (code ID-19/02260) and the instructions for use: once a day apply on facial skin, then apply a second time locally on the pigmented spots, for 28 consecutive days at home. On D28, the investigator or the clinical assistant under the responsibility of the investigator examined once again every volunteer and a questionnaire about the product's cosmetic properties was filled in by the subject at the end of the study. The depigmenting potential was evaluated by Mexametric measurements (Mexameter MX18, Courage & Khazaka GmbH, Cologne, Germany) after 28 days of application of the product. The trained evaluator assessed the subjective efficacy of the product on D1 and on D28 under standardised conditions. Photographs (face and profile view) were carried out on D1 and on D28.

Included subjects

22 female adult volunteers, with an average age of 58 years, between 43 and 70 years, with all type of skin and with pigmented spots on face, including one pigmented spot of 5 mm in diameter, were included and analysed.

Stand-Alone Treatment – Investigation Results

- **Assessment of dermatological tolerance:** at the end of the study, skin dryness was observed in two volunteers.
- **Assessment of depigmenting potential by mexametric measurements:**

	Melanic index (A.U.)					
	Pigmented treatment area		Non pigmented treatment area		Non pigmented untreated area	
	D1	D28	D1	D28	D1	D28
Mean	**188.9**	**174.8**	**124.4**	**117.6**	**87.7**	**90.0**
Standard deviation	47.7	47.5	31.4	31.2	34.7	32.7
Median	185.5	166.8	126.3	120.8	88.8	93.8
Minimum	130.0	104.0	65.5	50.5	25.0	29.5
Maximum	321.0	304.5	194.5	179.5	154.0	152.0
% of variation	**–**	**-7.5%**	**–**	**-5.5%**	**–**	**2.6%**
p value*	**< 0,000**		**0,002**		0,121	
Significance**	**S**		**S**		**NS**	

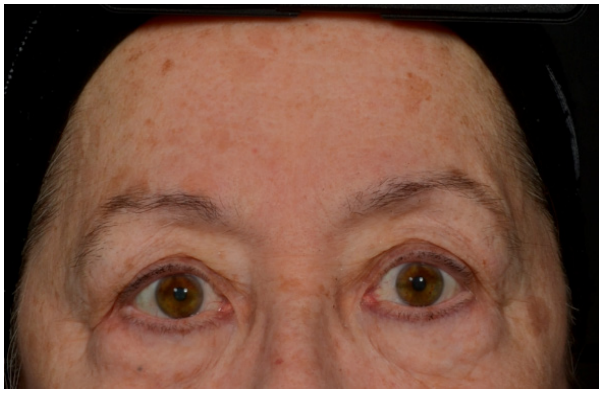
* Wilcoxon test for paired data: **S: Significant (p ≤ 0.05) — NS: Non Significant (p > 0.05)

Significant mexametric results on the average decrease of pigment spots (-7.5%) and the average decrease in dull complexion (-5.5%) which proves an overall depigmenting efficacy. Non-significant results on the non-pigmented and non-treated area proves that the volunteers were not exposed to the sun during the study. For reference purposes, these results are significantly above standard measurements and fall into the highest score band (20% above average).

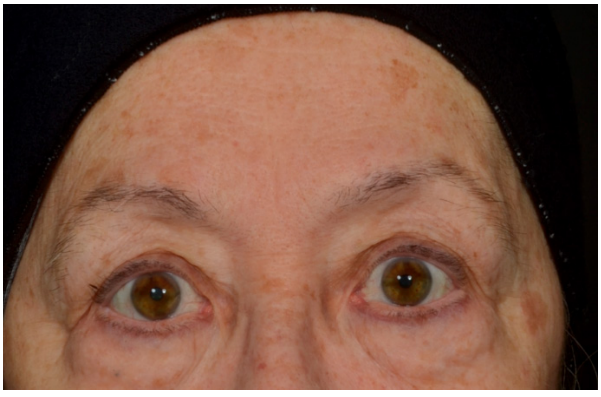
- **Assessment of cosmetic acceptability:** the volunteers had a good overall opinion of the Product.
  - ☑ 45% of volunteers found that the product reduced the appearance of pigment spots
  - ☑ 59% of volunteers found that their pigment spots were visibly lightened
  - ☑ 77% of volunteers felt that their complexion was more homogeneous
  - ☑ 68% of volunteers felt that their complexion was lighter

Before & After Photos: Highlighting the average decrease in pigment spots on the forehead:

Day 1



Day 28



Conclusion

Under the experimental conditions selected, the product exhibited:

- a depigmenting effectiveness demonstrated by Mexametric measurements;
- a subjective effectiveness of complexion uniformity and complexion radiance. And a lightening effect was also observed on the pigmented spot selected;
- an average dermatological tolerance, according to the adopted table, for facial skin;
- and an average cosmetic acceptability.

The study on the stand-alone treatment has shown exceptional results given its short duration (28 days) and the period in which it was conducted (March-April). Mela Cream has also been widely used as an in-clinic treatment booster, with outstanding results maintained over time and with maximum skin tolerance.

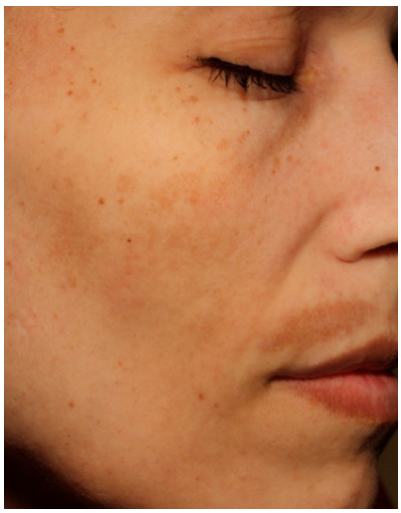
In-Clinic Treatment Booster

As a highly concentrated premium depigmenting cream, Mela Cream is proposed as part of an in-clinic treatment booster range of professional products applied following an aesthetic procedure (such as the Mela Peel or Mela Peel Forte). Prescribed extensively by expert practitioners, Mela Cream has demonstrated its high product efficacy and proven that it is a product doctor's trust.

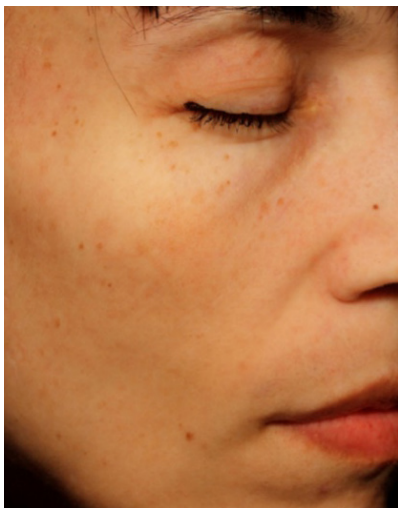
It is used by the patient at home for a recommended period, to boost and maintain treatment results.

Before & After Photos – Mela Peel
After 2 **Mela Peels** and Mela Cream used every night as part of the homecare protocol:

Day 0

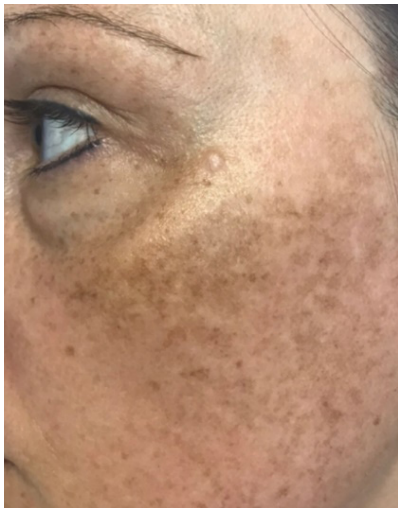


Day 42

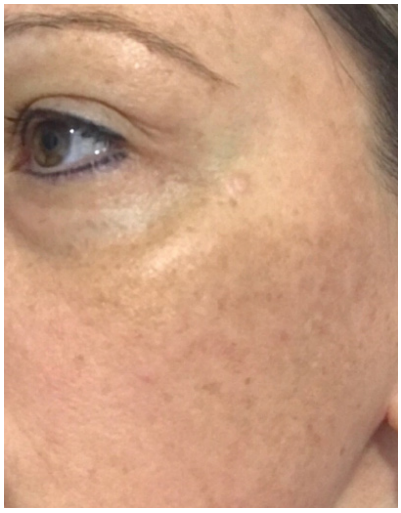


Before & After Photos – Mela Peel Forte
After 1 **Mela Peel Forte** and Mela Cream used every night as part of the homecare protocol:

Day 0



Day 30



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