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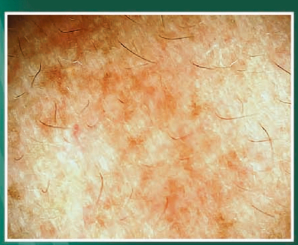
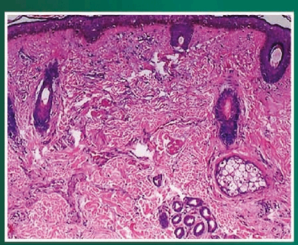
Melasma
A Monograph


2nd Edition

Editor
Rashmi Sarkar

Forewords
Amit G Pandya
Susan C Taylor

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MELASMA

A Monograph

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MELASMA

A Monograph

SECOND EDITION

Editor

Rashmi Sarkar MD MNAMS
Professor
Department of Dermatology
Maulana Azad Medical College and
Associated LNJP Hospital
New Delhi, India

Forewords

Amit G Pandya

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The Health Sciences Publisher
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Jaypee Brothers Medical Publishers (P) Ltd

Headquarters

Jaypee Brothers Medical Publishers (P) Ltd
4838/24, Ansari Road, Daryaganj
New Delhi 110 002, India
Phone: +91-11-43574357
Fax: +91-11-43574314
Email: jaypee@jaypeebrothers.com

Overseas Offices

J.P. Medical Ltd
83 Victoria Street, London
SW1H 0HW (UK)
Phone: +44 20 3170 8910
Fax: +44 (0)20 3008 6180
Email: info@jpmedpub.com

Jaypee-Highlights Medical Publishers Inc
City of Knowledge, Bld. 237, Clayton
Panama City, Panama
Phone: +1 507-301-0496
Fax: +1 507-301-0499
Email: cservice@jphmedical.com

Jaypee Brothers Medical Publishers (P) Ltd
17/1-B Babar Road, Block-B, Shaymali
Mohammadpur, Dhaka-1207
Bangladesh
Mobile: +08801912003485
Email: jaypeedhaka@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd
Bhotahity, Kathmandu
Nepal
Phone: +977-9741283608
Email: kathmandu@jaypeebrothers.com

Website: www.jaypeebrothers.com
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Dedicated to

My late father Professor (Dr) Asim Kumar Sarkar in proud remembrance

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Contributors

Editor

Rashmi Sarkar MD MNAMS
Professor
Department of Dermatology
Maulana Azad Medical College and Associated LNJP Hospital
New Delhi, India

Contributing Authors

Pallavi Ailawadi MD DNB
Senior Resident
Department of Dermatology
Maulana Azad Medical College and
Lok Nayak Hospital
New Delhi, India

Pooja Arora MD DNB
Associate Professor
Department of Dermatology
Dr Ram Manohar Lohia Hospital
and Post Graduate Institute of
Medical Education and Research
New Delhi, India

Shehnaz Z Arsiwala MD DDV
Consultant
Department of Dermatology
Saifee Hospital and
Prince Aly Khan Hospital
Mumbai, Maharashtra, India

Latika Arya MD
Consultant Dermatologist
L A Skin and Aesthetic Clinic
New Delhi, India

Anuva Bansal MBBS
Post Graduate Final year
Department of Dermatology
Maulana Azad Medical College and
Lok Nayak Hospital
New Delhi, India

Shivani Bansal MD DNB
Consultant Dermatologist
Kaya Skin Clinic
New Delhi, India

Jyotirmay Bharti DDV
Medical Director
Senior Consultant Dermatologist and
Aestheticican
Square Root Hair Transplant
and Skin Clinic
Gurugram, Haryana, India

Joyeeta Chowdhury MD
RMO-Cum-Clinical Tutor
Department of Dermatology
Nil Ratan Sircar Medical College
and Hospital
Kolkata, West Bengal, India

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Ncoza Dlova MBChB FCDerm PhD
Chief Specialist and Head
Department of Dermatology
University of KwaZulu-Natal
Durban, South Africa

Shilpa Garg DNB
Consultant
Department of Dermatology
Sir Ganga Ram Hospital
New Delhi, India

Narendra Gokhale MD
Consultant Dermatologist
Sklinic
Indore, Madhya Pradesh, India

Evangeline B Handog MD
Chair, Department of Dermatology
Asian Hospital and Medical Center
Consultant and Head
Cosmetic Dermatology Unit
Department of Dermatology
Research Institute for Tropical Medicine
Metro Manila, Philippines

Niharika Jha MD
Senior Resident
Department of Dermatology
Dr BC Roy Post Graduate Institute of Pediatric Science
Kolkata, West Bengal, India

Hee Young Kang MD PhD
Professor
Department of Dermatology
Ajou University School of Medicine
Suwon, Korea

Saloni Katoch MD
Consultant
Department of Dermatology, Venereology, and Leprosy
Dr KN Barua Institute of Dermatological Sciences
Guwahati, Assam, India

Nokubonga Khoza MBChB FCDerm
Honorary Consultant
Department of Dermatology
University of KwaZulu-Natal
Durban, South Africa

Maria Suzanne L Datuin-De Leon MD FPDS
Active Consultant
Department of Dermatology
St. Luke's Medical Center Global City
Taguig City, Philippines

Neha Meena MD
Dermatologist (DMO)
Central Hospital, North Western Railway
Jaipur, Rajasthan, India

Anisa Mosam MBChB MMed FCDerm PhD
Associate Professor and Principal Specialist
Department of Dermatology
University of KwaZulu-Natal
Durban, South Africa

Amit G Pandya MD
Professor, Department of Dermatology
University of Texas Southwestern Medical Center
Dallas, Texas, United States

Nilendu Sarma MD FAAD
Associate Professor and Head
Dr BC Roy Post Graduate Institute of Pediatric Science
Kolkata, West Bengal, India

Sumit Sethi MD DNB
Consultant, Department of Dermatology and Aesthetics, Venkateshwar Hospital
New Delhi, India

Sidharth Sonthalia MD DNB MNAMS FISD
Medical Director
Consultant Dermatologist and Dermatosurgeon, Skinnocence - The Skin Clinic and Research Centre
Gurugram, Haryana, India

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Foreword

The disfiguring stain of melasma continues to be a facial curse affecting millions throughout the world. It is now clear that psychological morbidity from melasma is significant. In this monograph, Dr Rashmi Sarkar and colleagues have produced a succinct and excellent treatise on this disorder, packed with important, up-to-date information on diagnosis and treatment. By reading this short booklet, physicians can expand their knowledge of melasma exponentially and apply this information immediately to the next melasma patient who walks through their clinic doors.

Virtually, all aspects of melasma are covered, including pathogenesis, topical creams, oral agents, peels, lasers, and impact on quality of life. Many studies have been reported recently in patients with melasma, therefore, this publication comes at a timely moment for all of us trying to treat patients with this disorder.

Amit G Pandya MD
Professor
Department of Dermatology
University of Texas Southwestern Medical Center
Dallas, Texas, United States

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Foreword

Melasma: A Monograph (2nd edition) is a comprehensive, informative, and to the point text on melasma. Professor Rashmi Sarkar has provided an invaluable tool to understand and treat this challenging disorder that has a significant psychosocial impact on patients, particularly in countries with unrelenting sun exposure. The monograph begins with the epidemiology, etiology, and pathogenesis of melasma and then moves on to discuss diagnostic tools before tackling diverse treatment interventions. *Melasma: A Monograph*, is easily and quickly digested and provides all the information that is necessary for medical students, residents, and attending physicians to diagnose and treat melasma.

Susan C Taylor MD
Associate Professor of Dermatology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania, United States

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Preface to the Second Edition

A monograph on melasma was the first book I had in mind when I thought of writing. But it stayed in the shelves of my mind quietly, till I coedited two other books. The idea of completing my pet project came back and with the good wishes of my colleagues who write on this topic, my mentors, and my family, I took up editing this book once again. For me, this book highlights my area of interest and research over the years and is very close to my heart. I have kept the format simple. It is a great joy to me to bring out its second revised edition with newer additions. So much has evolved that I have added fresher chapters and hope you find these useful.

I would like to thank my teachers in PGIMER, Chandigarh, India, who always laid special emphasis on "pigmentary disorders" and my mentors, Dr Amit G Pandya and Dr Pearl E Grimes, for making my dreams turn into reality by their encouragement at the American Academy of Dermatology. A word of thanks to Mr Vij at Jaypee Brothers Medical Publishers (P) Ltd., and especially Dr Neeraj Choudhary and Ms Barkha Arora who helped in the editorial process and were delightful to work with. A very big thanks to my family for always encouraging me in difficult times.

My patients of melasma and my students remain invaluable to me. As also the various eminent international and national authors, all friends, who came forward to contribute. I hope, you, the reader enjoys reading this book as much as I enjoyed editing it.

Rashmi Sarkar MD MNAMS
Professor
Department of Dermatology
Maulana Azad Medical College and Associated LNJP Hospital
New Delhi, India

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Preface to the First Edition

A monograph on melasma was the first book I had in mind when I thought of writing. However, it stayed in the shelves of my mind quietly, till I co-edited two other books. The idea of completing my pet project came back and with the good wishes of my colleagues who write on this topic, my mentors and my family, I took up editing this book once again. For me this book highlights my area of interest and research over the years and is very close to my heart. I have kept the format simple.

I would like to thank my teachers in PGIMER, Chandigarh, India who always laid special emphasis on "Pigmentary Disorders", my mentors, Dr Amit G Pandya and Dr Pearl E Grimes for making my dreams turn into reality by their encouragement at the American Academy of Dermatology and Dr Vijay Garg, the head of our department for his help and encouragement. A lot has been written on vitiligo but melasma has not received so much attention, hence that was how the idea of writing this "monograph" was born. A word of thanks to Mr JP Vij at Jaypee Brothers Medical Publishers (P) Ltd., and especially Dr Madhu Choudhary, Ms Shweta Tiwari, and Mr Manoj Kumar who helped in the editorial and designing process and were delightful to work with. A special note of appreciation to Dr Shilpa Garg for helping me in proof reading and editing. Lastly, I appreciate the encouragement from Mr Sathya Narayanan, Mr S Raghavendra, and Mr Sanket Paranjpe and the entire team of Galderma for their belief and support.

A word of thanks to my husband Dr Srikanta Basu and my son Abhik S Basu for prodding me on always. My patients of melasma and my students remain invaluable to me. As also the various eminent international and national authors, all friends, who came forward to contribute. I hope, you, the reader enjoys reading this book as much as I enjoyed editing and writing it.

Rashmi Sarkar MD MNAMS
Professor
Department of Dermatology
Maulana Azad Medical College and Associated LNJP Hospital
New Delhi, India

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CHAPTER 1

Epidemiology and Global Distribution of Melasma

Nokubonga Khoza, Ncoza Dlova, Anisa Mosam

INTRODUCTION

The accurate prevalence of melasma worldwide is unknown. This is attributed to the fact that melasma is a cosmetic problem and most patients may choose to consult their dermatologist privately.[1] Hence, a low prevalence of melasma is recorded in most public dermatology clinics. Unfortunately, these are not truly representative samples.[1,2] The prevalence of melasma remains unchanged in the past 3 years with recent literature stating variability between 1 and 50% depending on whether low or high-risk population.[3] According to the American Academy of Dermatology, melasma affects 5–6 million people, mostly women in the United States alone.[2-4]

There have been few studies that have randomly sampled the general population (Table 1).[4]

Although melasma affects all races, it is most prevalent among darker skin phototypes (Fitzpatrick skin III–V) and mainly found in patients of Hispanic, Latin Americans, Asians, Middle Eastern, and Africans descent; these have been the most studied groups (Fig. 1).[1-6]

Melasma was noted to be a common cutaneous disorder accounting for 0.25–4% of patients seen in dermatology clinics in South East Asia and was the most common pigment disorder among Indians. In the Hispanic population in Texas, Werlinger et al. noted the prevalence to be 8.8% with previous history of melasma in 4% patients.[4,7] In Iraq, melasma is also the most common dermatology problem accounting for 26.6% of Iraqi females. The polarity of melasma towards these ethnic groups is influenced by genetic and environmental factors, i.e. living in the areas of intense ultraviolet light exposure and the fact that physiologically darker skin produces larger amounts of melanin in response to solar radiation.[1]

Hexsel et al. noted that the occurrence of melasma in lighter skin phototypes, i.e. Fitzpatrick skin type II and III was influenced by the presence of family history in contrast to negative family history in Fitzpatrick's phototype IV and V.[8]

Table 1: Prevalence of melasma

Author	Location	Percentage of cases with melasma (%)
Sivayathorn	Thailand	33
Sarkar et al.	India	20.5 (in men)
Failmezger	Peru	10.1
Werlinger et al.	United States	8.8
Tomb and Nassar	Lebanon	3.4
Parthasaradhi and Al Gufai	Saudi Arabia	2.88
Hiletework	Ethopia	1.8

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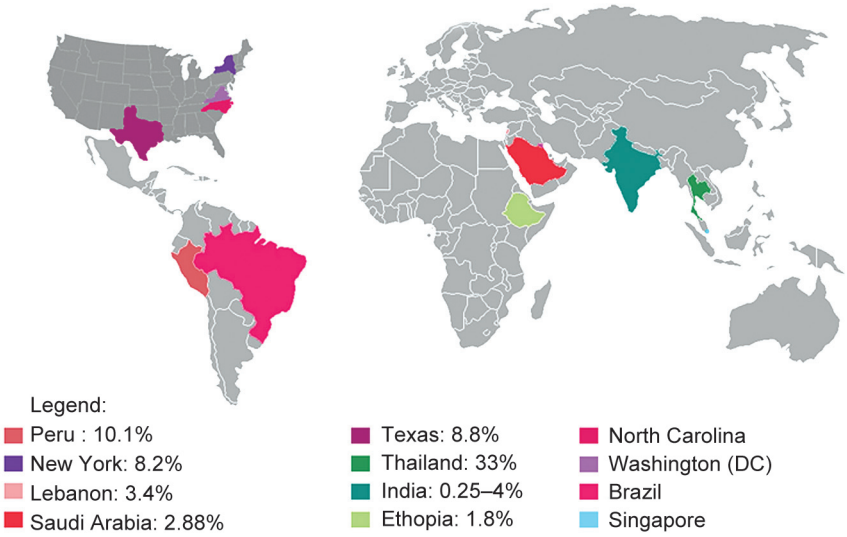

Figure 1: Schematic world map view of reported melasma prevalence and cases.

Melasma affects women more than men and occurs during child bearing age. The influence on age of onset have been thought to be related to a positive family history; first degree family having greater influence than the second degree, and supporting genetic factors in the development of melasma.[2] Krupashankar et al. also concluded that there is a strong correlation between family history and the prevalence of melasma amongst Indian population, this was highlighted by the regional variation in demographics and factors that precipitated melasma in three regions within India.[9] In the Brazilian population, familial melasma is noted with 50% of patients presenting with melasma having a first degree relative with the disease. In these patients, melasma was associated with long disease duration.[2] It was observed that family history of melasma was associated with early age of onset in not only Fitzpatrick's Skin types III to V but also skin type II.[2,8]

Male melasma is related to excessive ultraviolet light exposure, secondarily to occupational and other lifestyle issues in predisposed individuals. Pichardo et al. looking at melasma in immigrant Latino men (poultry processors and manual workers) noted that the prevalence of melasma in Latino men was 14.5% a bit higher than in women.[10] Melasma in these men occurred at a later age of onset 31 years or older. In those whose occupation involved high level of sunlight, presentation occurred at an earlier age.[10] Sarkar et al. also noted a prevalence of melasma to be about 20.5% in men in a prospective study in a tertiary care hospital, New Delhi, India.[11]

The relationship between melasma, pregnancy and hormonal influences in melasma has been documented. Most women with melasma report onset of disease during or after pregnancy or in relation to use of oral contraceptives. Pregnancy induced melasma is associated with early disease.[2] Few population-based studies that have looked at melasma have shown a varying prevalence of 10–70% suggesting that other factors like ethnicity and sun exposure are significantly involved.[2,5,12]

Although melasma is a common and easily diagnosed skin condition, better studies are required to address the worldwide epidemiology and prevalence.

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Editor's Note

Melasma is definitely among the top five leading dermatologic conditions in Asia. Ethnicity, genetic factors, and sun exposure play important roles. There are hardly any community-based studies and global data are mostly based on hospital-based studies.

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CHAPTER 2

Etiological Factors and Triggering Factors

Hee Young Kang

INTRODUCTION

Melasma is a common acquired hyperpigmentary disorder of the sunexposed area. It is widely accepted that it is more common in women and darker skin types such as Hispanics and Asians. Although the exact prevalence of melasma in general population is unknown, the reported prevalence of melasma ranges from 8.8% among Latino females in the Southern United States as high as 40% in Southeast Asian.[1] Melasma occurs in 10–15% of pregnant women and 10–25% of women taking oral contraceptives.[2,3] Men represent approximately from about 10% of patients as high as 23% in Indian melasma patients.[4,5]

ETIOLOGICAL AND TRIGGERIG FACTORS

The major etiological factors include genetic influences, chronic sun exposure, and female sex hormones.[5-9] A large global survey with 324 melasma women confirmed that the combination of the accepted triggering factors do affect onset of melasma.[6] In this study, the mean age at onset of melasma was 34 years (range 14–65 years) and Fitzpatrick skin phototypes III and IV were most commonly affected. Family history of melasma occurs in 50% of patients particularly with darker skin types such as African, American. The most common time of onset was after pregnancy (42%) with 26% during pregnancy. Only 25% of patients taking oral contraceptives had an onset of melasma after starting their contraceptive. It was suggested that melasma which first appears during a pregnancy is more likely to resolve spontaneously.[1] The study concludes that a combination of factors including ultraviolet exposure, family history, and hormonal disturbances are likely to play a role in the development of melasma. An epidemiologic study with 302 Brazilian melasma was performed and in these samples, melasma was also common in middle-aged woman with intermediate skin phototypes, Fitzpatrick skin phototypes III and IV.[7] A high familiar incidence of more than half the patients was reported supporting genetic factors that are important in developing melasma. It was noted that the patients who had positive family history had longer disease duration. The most commonly reported precipitating factors were pregnancy (36.4%), oral contraceptives (16.2%), and sun exposure (27.2%). It was noted that the pregnancy-associated melasma had earlier onset and was more common in those who had multiple pregnancies. In another multicenter study with 953 Brazilian melasma patients,[8] it was suggested that the age of melasma onset are related to skin phototypes and family history, i.e. Fitzpatrick skin phototypes II and III and positive family history of melasma had early onset of the melasma when compared with skin phototypes IV, V, and VI or absence of family history. The extra-facial melasma was more frequent in postmenopausal women. In an Indian study with 312 cases, a positive family history was observed in 33.3%, and about 55.1% of the patients had intense sun exposure.[9] In this study, only 22.4% of the

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patients reported pregnancy as a triggering or aggravating factor, and only 18.4% of them were taking oral contraceptives during their disease process. The study findings suggested that oral contraceptives or even pregnancy may not be a significant contributing factor in developing melasma. Another Indian study with 140 cases also showed that majority of patients were unskilled workers with an average sun exposure of more than 4 hours (44%).[5] Family history was observed in 18% cases. Very recently, the increased serum levels of malondialdehyde assay, superoxide dismutase assay, and blood glutathione in the serum of melasma patients were shown suggesting the role of oxidative stress in etiopathogenesis of melasma.[10]

CONCLUSION

In summary, above studies suggest that sun exposure and/or hormonal stimuli may trigger melasma development in patients who have intrinsic sensitivity to those stimuli. The high incidence of family history in melasma patients suggests that they have a genetic component. The sun exposure and hormonal stimuli are commonly reported triggering factors in those studies. The prolonged sun exposure could stimuli upregulation of certain melanogenic factors in the melasma skin. The presence of local hormones in the skin may play a role in the development of melasma although the exact mechanism is still unclear. It is possible that certain effects induced by sex hormones in the patients required additional synergistic events in addition to sun exposure to develop melasma.

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CHAPTER 3

Etiopathogenesis of Melasma

Sidharth Sonthalia, Jyotirmay Bharti

INTRODUCTION

Melasma, one of the most common hyperpigmentary disorders known, is a frustrating condition. Relapse is invariable despite optimum preventive measures and dermatologists can only ensure "treatment and maintenance" of effect rather than "permanent cure." Despite continuous quest for the etiological factors and pathogenetic mechanisms contributing to melasma, its pathophysiology remains elusive and treatment challenging. Over the last one-decade, new findings based on advanced techniques like dermoscopy, *in vivo* reflectance confocal microscopy (RCM), and immunohistochemistry from biopsy specimens have provided sufficient insight into its pathogenesis. While old time-tested theories regarding its pathophysiology have not yet been discarded, recent and emerging postulates need further confirmation. Two groups of factors seem to be instrumental: (i) "endogenous factors," most importantly genetic predisposition and cutaneous vasculature and (ii) "exogenous stimuli" such as sex hormones and ultraviolet (UV) irradiation, respectively.

EPIDERMAL HYPERPIGMENTATION: THE MAIN CULPRIT

Melasma has traditionally been classified into epidermal, mixed, and dermal. This differentiation by Wood's lamp examination has been *in vogue* with features of epidermal, dermal, and mixed type of melasma being accentuation of lesional pigmentation, lack of enhancement of lesional pigment, and presence of both enhancing and nonenhancing areas, respectively. However, this concept seems redundant with a recent *in vivo* RCM study that demonstrated heterogeneous distribution of melanophages between different regions of the melasma lesion and within a particular region of a melasma lesion. These findings raise serious doubts about the existence of "true epidermal" or "true dermal" melasma and suggest that all melasma are indeed mixed.[1] Epidermal hyperpigmentation through increased melanogenesis in epidermal melanocytes is now considered to be the hallmark of melasma lesional skin, evidenced by an 83% increase in epidermal pigmentation in the lesional skin of 56 Korean patients, and confirmed on RCM.[1,2] Thus, melasma is chiefly characterized by epidermal hyperpigmentation with or without melanophages. The role of small amount of dermal melanin in the melasma lesional skin remains speculative.

MELANOGENESIS AND HYPERACTIVE MELANOCYTES: INSIGHTS FROM HISTOLOGICAL AND RCM STUDIES

Histopathology of melasma lesions has offered valuable insights to understand its etiopathogenesis. In the study by Kang et al. (*vide supra*) comparing the histology of melasma lesions and normal facial skin, the following features were more pronounced in the

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former—solar elastosis, greater number of epidermal melanocytes, dermal-free melanin and melanophages, elastic fiber fragmentation, and significantly increased epidermal melanin.[2] The melanocytes in lesional skin have been found to be pendulous and biologically more active than their counterparts in normal skin with increased dendriticity and presence of greater quantities of mitochondria, Golgi, and rough endoplasmic reticulum.[3] While enhanced melanogenesis within these melanocytes of melasma lesions has been proven by recent findings of upregulation of many melanin biosynthesis-related genes and melanocytes markers like tyrosinase, TYRP1, TYRP2, and MITF, whether melanocytosis contributes to it is still controversial.[1-3] Apart from increased basal layer hyperpigmentation, the dermis reveals sparse to moderate mononuclear infiltrate, melanophages, and solar elastosis (Fig. 1). Presence of mast cells and increased dermal vascularity are also observed on histology of melasma lesions. Although, abnormalities of the dermal ECM have been commonly observed in melasma, the role of these alterations in the pathogenesis of melasma has gained recognition only recently. Solar elastosis, an archetypical feature of photo-aging characterized by prolonged sun exposure-induced accumulation of abnormal elastic tissues in the dermis is a frequent histological feature in melasma skin. A significantly higher degree of solar elastosis was observed in lesional melasma skin compared with perilesional skin (83% *vs.* 29%, $p < 0.05$).[4] The histological findings of melasma have been corroborated by RCM, which allows evaluation of melasma at the cellular level. The hyperpigmented basal keratinocytes appear as increased hyper-refractile cobblestoning cells, activated melanocytes present as epidermal dendritic cells, and melanophages look like plump bright cells on RCM.[5]

MULTIFACTORIAL ETIOPATHOGENESIS OF MELASMA (FIG. 2)

The major etiological factors implicated in melasma seem to act in concert. In a study of 210 patients, the incidence of different causative factors was 100% for sunlight exposure, 27% for pregnancy, 14% for cosmetics, 13% for familial factors, and 6.3% for oral contraceptive pill (OCP) use.[6] The results of a recent global survey by Ortonne et al. in 324 women with melasma also suggest that a combination of hormonal factors such as pregnancy and OCP use and sun-exposure are involved.[7]

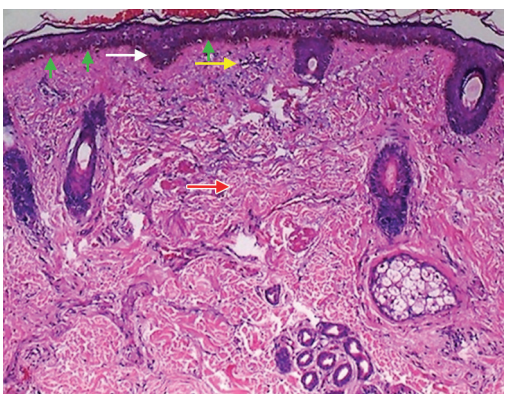

Figure 1: Histopathology of a melasma lesion revealing preservation of rete ridges, epidermal hyperpigmentation clustered in the basal layer (white arrow), superficial dermal perivascular infiltrate predominantly of melanophages (yellow arrow) and widespread solar elastosis (red arrow). Additionally, note the focal disruptions in the basement membrane (green arrows) [H&E, 400×].

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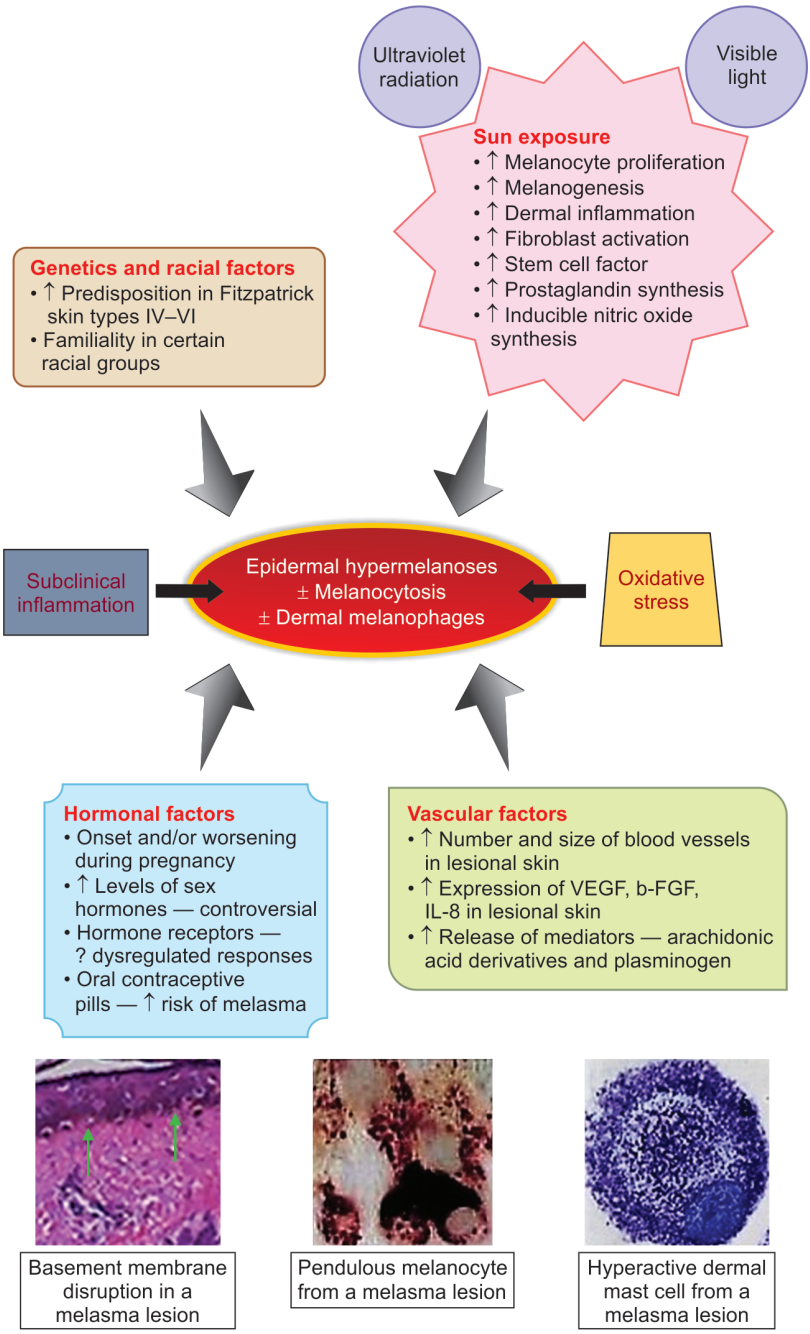

Figure 2: Major etiological factors of melasma with mechanisms associated with them.

GENETICS AND RACIAL FACTORS

A genetic predisposition is suggested by a high reported incidence in family members of certain racial groups. It has ranged from 10% to up to 70% in studies from Iran, Singapore, and in Latino men.[8] In Southeast Asia, the prevalence ranged from 40% in females and 20%

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in males.[9] The Global survey by Ortonne et al. comprising of women from nine countries reinforced the susceptibility of Fitzpatrick skin phototypes III and IV and a higher likelihood of a positive family history in African-Americans.[7] Although, genome-wide studies have not been performed to examine the associated genes, it has been suggested that the genes responsible involve pigmentary, inflammatory, hormonal, and possibly vascular responses.[10] The precise underlying molecular mechanisms need to be elucidated.

ROLE OF SUN EXPOSURE

Facts Suggesting the Relationship of Melasma with Sun Exposure

Sunexposure, especially UV radiation (UVR) is undoubtedly the most important etiological factor for melasma. Occurrence of lesions in predominantly sun-exposed areas of the face and delay in relapse after successful reduction with regular use of broad-spectrum sunscreens support the role of unimpeded sunexposure in evolution and progression of melasma. Moreover, features of solar damaged skin, typically solar elastosis on histology, are often present in lesions of melasma.

Cellular and Humoral Mechanisms Underlying Ultraviolet-induced Melasma

Complex cellular interactions and interplay of cytokines and hormones contribute to the effect of UVR in melasma. Latest evidence has implicated cells other than melanocytes notably, keratinocytes, dermal fibroblasts, and cutaneous vasculature.[11]

- *Effects of UVR on keratinocyte-melanocyte interaction*: UV irradiation stimulates melanogenesis by direct effects on melanocytes and by indirect effects on keratinocytes that release melanogenic factors. Direct activation involves the formation of endogenous 1,2-diacylglycerols' (DAGs), protein kinase C-beta activation, and production of nitric oxide (NO) and cGMP. Ultraviolet-induced paracrine stimulation of melanocytes via keratinocytes includes melanogenic factors like basic fibroblast growth factor (bFGF), nerve growth factor (NGF), endothelin-1 (ET-1), and the pro-opiomelanocortin (POMC)-derived peptides such as melanocyte-stimulating hormone (MSH) and adrenocorticotrophic hormone (ACTH) (Fig. 2).[12] These peptides stimulate melanocyte proliferation as well as melanin synthesis via stimulation of tyrosinase activity and tyrosinase-related protein 1 (TRP-1).[13] The interaction of melanocortin (MC) and MC-1 receptor (MC1R) upregulates melanogeneis through the intracellular cAMP signal transduction-protein kinase A (PKA) activation pathway and microphthalmia-associated transcription factor (MITF), particularly the MITF-M isoform. The enhanced expression of inducible nitric oxide synthase (iNOS) in melasma within keratinocytes also contributes to the melanogenesis process.[14]
- *Effects of UVR on dermal inflammation and fibroblast activation*: Kang et al. have reported significantly increased expression of both stem cell factor (SCF) from fibroblasts and c-kit in the melasma lesional skin.[15] The cytokines derived from fibroblasts stimulate the proliferation and melanogenesis of melanocytes. Thus, the UV-induced dermal inflammation leading to fibroblast activation resulting in upregulation of SCF in the dermis of melasma lesions, culminating into increased melanogenesis sounds like a plausible explanation. Other inflammatory events operating at the cellular level may also have a role. Ultraviolet-stimulated synthesis of prostaglandins (PGs) and upregulation of cyclooxygenase-2 (COX-2) in lesional skin resulting in epidermal hyperpigmentation has been reported.[2] The emergence of PG analogs as a therapeutic option for vitiligo lends further support to this speculation.

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- *Visible light and melasma*: Apart from the effect of UVR, the role of visible light is being increasingly recognized. Visible light is known to induce hyperpigmentation especially in skin types IV–VI.[16] It could explain the only partial protective effect of most UV-A and UV-B protective sunscreens and higher efficacy of tinted mineral sunscreens that additionally protect against visible light in prevention of melasma relapses.
- *Other UV-induced mechanisms*: Ultraviolet light also stimulates melanogenesis by inducing basement membrane (BM) disruption, abnormalities in the extracellular matrix (ECM), and mast cell activation *(vide infra)*.[17]

BASEMENT MEMBRANE DISRUPTION: A RELATIVELY RECENTLY DETECTED FEATURE OF MELASMA

Recent research has focused on the presence and role of focal vacuolar degeneration of the basement membrane in melasma. Although there is a huge variation in the reported incidence of BM disruption in melasma depending on the study population (3–95.5%), it is considered as a key feature that further bridges the relationship between chronic UV exposure and melasma.[17] Pendulous melanocytes associated with basement membrane abnormalities were demonstrated as a characteristic feature of melasma (Fig. 2).[18] In a recent study of melasma patients with Fitzpatrick skin types IV and V, a disrupted BM was observed in 95.5% and 83% of skin samples via periodic acid-Schiff-diastase (D-PAS) staining and anti-collagen type IV immunohistochemistry, respectively.[4] Chronic UV exposure-induced elevated levels of matrix metalloproteinase (MMP)-2 and MMP-9 degrade type IV collagen and type VI collagen in the skin, resulting in BM disruption.[19] Recently, UV-independent pathways leading to BM disruption in melasma lesions have been discovered. It has been suggested that Cadherin 11 (CDH11) overexpression could induce BM disruption and dermal changes in melasma, regardless of UV exposure.[20] The disruption of BM also explains the descent of melanocytes and melanin into the dermis, which appear as free melanin or melanophages in the dermis of melasma (Fig. 1) skin thereby rendering melasma refractory to treatment and prone to relapse.[4,17]

ROLE OF DERMAL MAST CELLS

Compared to the perilesional skin, the lesional melasma skin has demonstrated significantly higher number of dermal mast cells.[4,21] Release of various inflammatory mediators from dermal mast cells is upregulated in response to UV irradiation:

- Histamine stimulates the melanocyte proliferation and migration mediated by H2 receptors, with a suspected role of the growth-differentiation factor-15, a member of transforming growth factor-β (TGF-β) family[21]
- Mast cell tryptase activates pro-MMP-9 and degrades type IV collagen. It contributes to ECM proteins damage and weakening of the BM directly as well as through the release of other cytokines[21]
- Granyme B, a serine protease expressed by increased mast cell population, also contributes to ECM degradation in the skin after UV irradiation[21,22]
- Secretion of angiogenic factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), and TGF-β contribute to vascular dilatation.[21,23]

Thus, it is likely that mast cells may initiate epidermal pigmentation of melasma through direct stimulation of melanocyte proliferation, disruption of BM, damage to ECM and promotion of abnormal angiogenesis.

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ROLE OF HORMONES

The relationship of melasma with female sex hormones, OCPs, and pregnancy has been perplexing and needs further elucidation.

Pregnancy and Melasma

Many patients note the onset or worsening of melasma during pregnancy; often christened as "chloasma gravidarum" and "the mask of pregnancy" with typical onset during the second half of the gestational period. However, melasma may appear before pregnancy or many years after delivery. The reported incidence of melasma appearing during pregnancy has ranged from 2.5 to 75% with a reported higher incidence in pregnant women with the skin of color (SOC). The onset or worsening of melasma during pregnancy is most commonly encountered in women of black, Hispanic, or Asian descent. Major studies on epidemiology of melasma in Indian women are lacking; however, two studies have reported an incidence of 2.5–8.5% during pregnancy in Indian women.[24,25]

Oral Contraceptive Pills and Melasma

The onset of melasma following intake of OCPs is well-documented. In the global survey by Ortonne et al., 25% of 324 women with melasma reported disease onset with OCP use.[7] Occurrence of melasma has been reported in 11.3–46% of individuals who used oral contraceptives in different countries, including Singapore, Iran, India, Tunisian, and Brazil.[12]

The accrued evidence from different studies studying the epidemiology of OCP-induced melasma suggests it to be more common in patients lacking family history of melasma and a higher risk of recurrence or worsening of melasma during pregnancy in such patients. Thus, while patients who develop melasma while taking OCPs may benefit by stopping them and avoiding them in future, a systematic change in hormonal contraception in melasma patients seems unwarranted.[8,12]

Hormones, Hormone Receptors, and Melasma

With respect to female sex hormones, estrogens and progesterones have been implicated in the development of melasma, although the extant studies have reported conflicting results. One of the major limitations of exploring this association stems from the wide variation of results reported from studies conducted in varied genetic and ethnic study populations, which may have different sex hormone metabolizing enzyme milieu. While studies from the Indian subcontinent have reported significant increase in estradiol levels (both in the follicular and in the luteal phases) in patients with melasma, compared to the controls, contradictory results have been reported by other authors.[12,16,26,27]

Recent credence to the pathogenetic role of estrogens in melasma has been lent by a literature-search based preliminary suggestion of a possible association between improvement of melasma in patients with oligomenorrhea associated with a hyperestrogenic state with systemic anti-estrogenic therapy, and anecdotal reports of development of extrafacial melasma following topical estrogen application, reduction of melasma following application of anti-estrogen cream, and development of melasma in Caucasian men following treatment with finasteride.[28-31] Although, hormonal pathogenesis of melasma in men lacks robust evidence, increased levels of luteinizing hormone and reduced levels of testosterone have been reported in Indian men with melasma.[32,33]

With lack of clarity on the role of levels of circulating levels in pathogenesis of melasma, the role of hormone receptors has become an active area of research. The practical impact

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Table 1: Proposed mechanisms of melanogenesis stimulation by estrogen-estrogen receptor interaction in the pathogenesis of melasma[12]

Mechanism	Effect
Direct induction of protein synthesis	Upregulation of tyrosinase, TRP-1, TRP-2, MITF
Activation of the cAMP-PKA pathway	Upregulation of tyrosinase
Overexpression of *PDZK1* gene (present in keratinocytes, melanocytes)	Enhanced tyrosinase expression and melanosome transfer
Increased expression of MC1R in melanocytes	Upregulation of tyrosinase via cAMP-PKA pathway stimulation

cAMP-PKA, cyclic adenosine monophosphate-protein kinase A; MC1R, melanocortin type 1 receptors; PDZK1, PDZ domain protein kidney 1; TRP-1,2, tyrosinase-related protein 1,2.

of increased expression of progesterone receptor (PR) in melasma lesional skin remains ill-understood and needs further exploration. Immunohistochemical studies have shown that compared to melanocytes of nonlesional skin, cells from melasma lesions exhibit increased estrogen receptor (ER) expression. Based upon cultured melanocyte studies, at least four mechanisms have been hypothesized to be involved in the estrogen-ER interaction induced hypermelanogenesis (Table 1).[12]

In conclusion, factors such as heightened sensitivity of melanocytes of melasma lesions to estrogens (and possibly other hormones) and additional synergistic influences such as UVR, cutaneous vasculature, activity of sebaceous glands, and oxidative stress need to be analyzed collectively.[8] This conclusion is clearly backed by the relative failure of any anti-melasma treatment that targets just one aspect of the pathogenesis. It is well known that treatment with sunscreens and depigmenting agents often provide suboptimal and short-lasting improvement only.

VASCULAR FACTORS

- The demonstration of more prominent solar elastosis in lesional melasma skin compared with perilesional skin, and UV-induced dermal inflammation leading to fibroblast activation and resultant increase in melanogenesis makes a strong case for the role of dermal environment in development of melasma.[2,15] Apart from the role of dermal components such as the ECM, fibroblasts, and mast cells in enhancement of melanogenesis through paracrine effects over the melanocyte-keratinocyte unit (*vide supra*), there is a newfangled interest in the role of cutaneous vasculature in its pathogenesis. Though hyperpigmentation predominates the clinical presentation of melasma, many patients demonstrate additional distinguishing feature of pronounced telangiectatic erythema confined to the melasma lesional skin (Fig. 3) although the perilesional skin may also show increased erythema.[34] Evidence from recent research including results of colorimetric analysis, immunohistochemical studies, and laser confocal microscopy examination has shown that melasma lesions are more vascularized than the perilesional skin.[8,15,34-36] These changes, however, even if present are often missed on naked eye examination but may be appreciated on dermoscopy (Fig. 4).[37] The increased vascularity is even more easily discernible with the use of advanced instruments like the chromameter and spectrocolorimeter.[35,36] The investigative study conducted by Kim et al. in 50 women with newly-diagnosed melasma provided robust evidence to support the vascular theory of melasma and probable events involved in it. They demonstrated: (i) significant increase in both the number and size of dermal blood vessels and (ii) upregulated expression of vascular endothelial growth factor (VEGF), in the lesional skin

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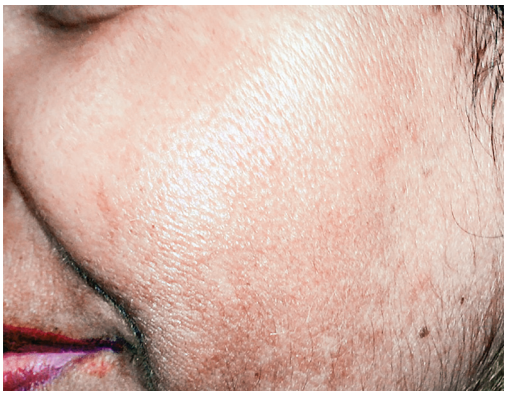

Figure 3: Clinical appearance of an untreated patient with melasma showing pronounced telangiectatic erythema interspersed with hyperpigmented macules.

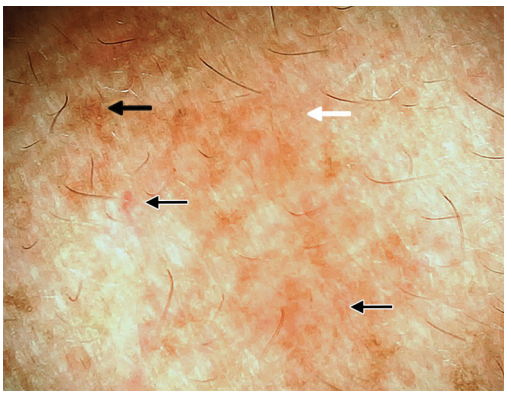

Figure 4: Dermoscopic appearance of the patient in Figure 3, demonstrating patchy hyperpigmentation (solid black arrow), prominent interspersed erythema (solid white arrow), and multiple telangiectasias (black arrow with white margins) (Escope video dermatoscope, polarized mode, original magnification ×20).

compared to the perilesional normal skin.[34] It has been speculated that UV irradiation induces an angiogenic switch, associated with the upregulation of proangiogenic factors such as VEGF, basic fibroblast growth factor (b-FGF), and interleukin (IL)-8. Vascular endothelial growth factor is the major putative angiogenic factor and it seems to enhance melanogenesis by interaction with VEGF receptors present in epidermal keratinocytes followed by release of mediators, most importantly metabolites of arachidonic acid, and plasminogen from the proliferated vessels.[15,34] The role of increased dermal mast cells leading to the secretion of angiogenic factors (VEGF, FGF-2, and TGF-β) that contribute to vascular dilatation has already been mentioned.[21,23] Finally, the reports of moderate efficacy of two newer treatment modalities, i.e. tranexamic acid (TEXA), a plasminogen inhibitor, and pulsed dye laser (PDL) that primarily target vascular components of the skin, further lend support to the vascular theory of melasma.[35,36]

However, it is prudent to be cognizant of the fact that:

- Not all patients would benefit from therapies-targeting the vascular arm of melasma pathogenesis. Only those patients with melasma are likely to benefit, who have definite

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evidence of increased vascularity. The same can now be ascertained based on close naked eye examination, dermoscopy, and colorimetry-based techniques. Lastly, patients who have repeatedly failed on treatments targeting only pigmentary component of melasma may benefit.

- The use of PDL in SOC, especially in skin types IV-VI, should be undertaken after confirming patient's suitability (based on a prominent vascular component), and laser parameters should be light and non-aggressive. In one study that evaluated the efficacy of the copper bromide/yellow laser (578 and 511 nm) in Thai female melasma patients with skin phototypes III–V found no effectiveness after six 2-weekly treatments; and any mild improvement reversed within days of the last session. Regrettably, adverse effects were encountered in almost all the patients and included burning sensation, scaling, crusting, and postinflammatory hyperpigmentation (PIH).[38]
- Although the results of oral, microinjected, and topical TEXA have by and large been encouraging in melasma, especially in the Asian and Asian-Indian population, the exact mechanism of this plasminogen inhibitor is still not well-known. Postulates include (i) direct inhibition of tyrosinase, (ii) anti-inflammatory effect, (iii) decreased dermal vessel number, (iv) inhibition of UV-induced plasmin activity in keratinocytes resulting in decreased free arachidonic acid and a diminished ability to produce PGs, which in turn decrease melanocyte tyrosinase activity, (v) reduction of dermal mast cells, whose role in promoting melanogenesis has been discussed (*vide supra*), and (vi) suppression of ET-1, well-known UV-inducible melanogenic factor, which is thought to be secreted from keratinocytes.[34-36,39]

SUBCLINICAL INFLAMMATION IN MELASMA: EVOLVING ROLE OF CYCLOOXYGENASE-2 AND INTERLEUKIN-17

We have discussed at length the mechanisms involved in pathogenesis of melasma from its major etiological factors, light exposure, hormone-receptor interaction, and vascular abnormalities. Further, the microanatomical abnormalities that have recently come to light as probable harbingers of melasma evolution, including pendulous and overactive melanocytes, BM disruption, increased dermal mast cells, and signals from abnormal dermal ECM have also been discussed. In addition to these, the phenomenon of subclinical inflammation preceding the evolution of melasma merits attention. This arm of melasma pathogenesis is not exclusive, rather it seals the interconnection of the other implicated factors. Histologically, other than the features of melasma which have already been discussed, one feature needs more in-depth evaluation; the presence of a moderate lymphohistiocytic infiltrate in the dermis from lesional skin. Photo-induced inflammation might be involved in epidermal pigmentation through COX-2-induced secretion of prostaglandins by keratinocytes, a mechanism typically implicated in the pathogenesis of PIH.

In a recent study conducted in 20 healthy Mexican female patients with naïve malar melasma of onset within 2 years (with no history of any topical or sunscreen use in the last 4 weeks, and hormonal or anti-inflammatory therapy in the last 8 weeks), lesional and extra-lesional skin biopsy samples were subjected to histochemistry with special stains for melanin, mast cells and elastin fibers, immunohistochemistry for different cluster of differentiation (CD) and various ILs, especially IL-17, in addition to quantitative real-time polymerase chain reaction.[40] The increased lymphocytic infiltrate in lesional skin was mainly composed of CD4+ T cells, CD68+ macrophages, and mast cells. The levels of IL-17 and COX-2 were significantly elevated in affected skin compared with healthy skin. Interleukin-17, produced by Th17 cells (differentiated from CD4T cells) in response to environmental or microbial antigens presented by activated dendritic cells in the epidermis binds to its receptors,

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primarily located on the surface of keratinocytes. This seems to trigger off synergistic activation of various pathways that culminate into production of chemokines, cytokines, and other proinflammatory mediators, like COX-2.[41] Production of COX-2, the inducible form of COX increases manifold following repeated UV exposure-induced upregulation of the prostaglandin PGE2. Thus, the presence of high levels of IL-17 in melasma lesions may be a key factor responsible for persistence of melasma, the local inflammatory responses being amplified and propagated by COX-2.[40] In this study, the Melasma Activity and Severity Index (MASI) score and epidermal melanin showed a positive correlation with the number of CD4+ T cells and COX-2 expression.

In summary, chronic UV exposure may initiate recruitment of naïve CD4 T cells to the affected areas, followed by their differentiation into IL-17-producing cells. The IL-17 load might trigger inflammatory responses in keratinocytes and maintain melanogenesis via production of COX-2, which could directly or indirectly promote melanin synthesis. The improvement in melasma with 4% topical niacinamide (an anti-inflammatory agent) comparable to that achieved with 4% hydroquinone supports the inflammatory hypothesis of melasma pathogenesis.[42]

OXIDATIVE STRESS IN MELASMA

This aspect of melasma pathogenesis is perhaps the most recent and mandates further exploration. In a case-control study conducted in 2014 (50 melasma patients, 50 healthy volunteers), the levels of superoxide dismutase (SOD), and glutathione peroxidase enzyme activities were significantly higher in the patient group compared to controls, while protein carbonyl levels were significantly lower in the patient group ($p < 0.001$); supporting higher levels of oxidative stress in melasma patients.[43]

In our own experience of our recently published case-control study conducted in 50 Indian patients with melasma, we found statistically significant higher serum levels of malondialdehyde, SOD, and blood glutathione (markers of oxidative stress) in cases than controls. Further, in melasma cases, a significant positive correlation was observed between serum malondialdehyde and the severity of melasma determined by the modified MASI score.[44] In one trial involving 30 women with melasma, who were administered 75 mg pycnogenol (a strong oral antioxidant derived from the bark of French maritime pine) daily for 30 days, an overall effective improvement rate of 80% was reported by the researchers.[45] Although the results from these studies endorse a clinically significant role of oxidative stress in melasma, carefully designed mono-antioxidant therapy-based clinical-cum-biochemical therapeutic trials are warranted for confirmation of these results.

A schematic depiction of the major pathogenetic mechanisms involved in the evolution of melasma in given in figure 5.

OTHER FACTORS

Various other factors have been implicated in the pathophysiology of melasma (Table 2).[46] However, the evidence supporting their definitive role is weak and controlled studies are warranted to establish their contribution to the causation of melasma.

MOLECULAR PATHOGENESIS

The precise molecular pathogenesis of melasma remains mysterious. Results of a transcriptional analysis study performed in lesional skin samples compared with normal skin have provided interesting insights into its complex pathophysiology. Of the total 279 genes stimulated in

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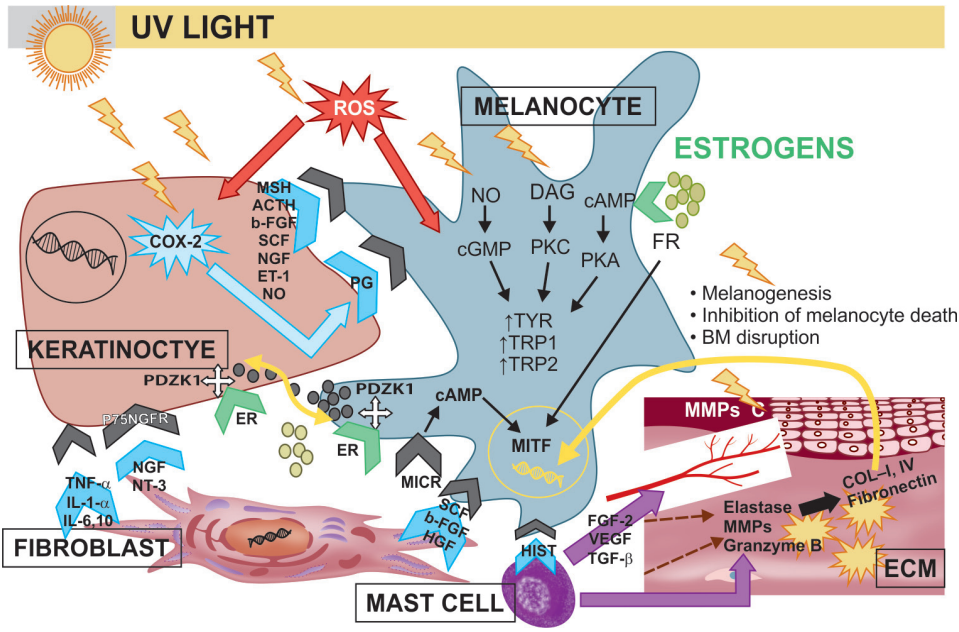

ACTH, adrenocorticotrophic hormone; BM, basement membrane; b-FGF, b-fibroblast growth factor; cAMP-cyclic AMP; COL, collagen; COX-2, cyclooxygenase-2; DAG-diacylglycerol; ECM, extracellular matrix; ER, estrogen receptors; ET-1, endothelin-1; FGF-2, fibroblast growth factor-2; HGF, hepatic growth factor; HIST, histamine; IL, interleukin; MC1R, melanocortin type-1 receptors; MITF, microphthalmia-associated transcription factor; MMP, matrixmetalloproteinases; MSH, melanocyte stimulating hormone; NGF, nerve growth factor; NGFR, nerve growth factor receptor; NO, nitric oxide; NT-3, neurotrophin-3; PG, prostaglandins; PKA - protein kinase A; PKC - protein kinase C; ROS, reactive oxygen species; SCF, stem cell factor; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; TYP, tyrosinase-related protein; TYR, tyrosinase; VEGF, vascular endothelial growth factor

Figure 5: Schematic representation of the major pathogenetic mechanisms involved in melasma.

this study, 152 were found to be downregulated, with upregulation of many melanogenesis-related genes and melanocyte markers such as TYR, MITF, SILV, and TYRP1.[47] Interestingly, certain genes involved in other biological processes and/or expressed by cells other than melanocytes were found to be differentially expressed in lesional skin, especially a subset of Wnt pathway modulator genes (Wnt inhibitory factor 1, secreted frizzled-related protein 2, and Wnt5a), genes of PG metabolic processes, and those regulating lipid metabolism. Noncoding ribonucleic acid (RNA) also seems to participate in the pathogenesis of melasma. In a recent melanocyte-keratinocyte culture study, the *H19* gene which transcribes a noncoding RNA was found to be significantly downregulated in lesional skin.[48] Stimulation of melanogenesis and increased transfer of melanin to keratinocytes were associated with decreased transcription of *H19* suggesting the role of this gene in evolution of melasma.

The most affected biological process in melasma is lipid metabolism which seems to be the most affected biological process in the pathogenesis of melasma.[47,49] Genes involved with lipid metabolism, such as peroxisome proliferator-activated receptor (PPAR)-α, arachidonate 15-lipoxygenase, PPAR- γ co-activator 1α, type B (ALXO 15B), diacylglycerol O-acyltransferase 2-like 3 were found to be downregulated; seemingly due to chronic UV exposure.[1] Another change observed in melasma skin is thinning of the stratum corneum; which coupled with disturbed lipid metabolism is responsible for the impaired integrity of stratum corneum resulting in the delayed barrier recovery rate seen in melasma skin.[50] Other

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Table 2: Minor factors associated with melasma

Causative factors	Association with melasma and possible mechanism
Thyroid disorders	The frequency of thyroid disorders is four times greater in patients with melasma. More commonly associated with hormone-associated melasma
Cosmetics	Photoactive contaminants of mineral oils, petrolatum, beeswax, some dyes, para-phenylenediamine, and perfume ingredients may be involved. While some cases of cosmetic-induced facial hyperpigmentation may actually represent Poikiloderma of Civatte, the role of cosmetic ingredients (in synergism with UV exposure) in causation of melasma cannot be ruled out
Drugs	Phototoxic and photoallergic drugs, e.g. medications containing metals such as arsenic, iron, copper, bismuth, silver, and gold; antiseizure drugs; and organic compounds such as quinacrine have been associated with generalized hyperpigmentation and may be involved with development of melasma
Infection	*Chlamydia trachomatis*-induced photosensitivity in patients with clinical or subclinical genitourinary may be contributory, confirmed by the presence of antichlamydia IgM antibodies in many patients with melasma
Stress	Sudden and profound emotional stress implicated in two reports. Release of MSH by the hypothalamus in response to stress is the postulated mechanism
Melanocytic and lentiginous nevi	Patients with melasma tend to show significantly higher number of both types of nevi compared to controls. This indicates a possible relationship between melasma and the overall presence of hyperpigmentary aberrations
Neural component	Increased numbers of keratinocytes expressing nerve growth factor receptor and hypertrophic nerve fibers in the superficial dermis of lesional skin are suggestive of a neural component

UV, ultraviolet; IgM, immunoglobulin M; MSH, melanocyte stimulating hormone.

molecular pathways have also been implicated. Ultraviolet radiation-induced activation of iNOS expression within keratinocytes (*vide supra*) contributing to the melanogenesis process could be linked to an activation of the AKT/nuclear factor-κB pathway.[14,46]

CONCLUSION

Though the exact role of etiological factors in causation of melasma and its precise pathogenesis remain puzzling, newer studies have provided corporeal evidence in favor of certain previously suspected and some novel factors. Active research on melasma pathogenesis is addressing the vascular aspects, inflammatory aspects, and the role of oxidative stress. Further research in this area will not only provide more evidence for their involvement in the pathophysiology of melasma, but also offer attractive targets for development of newer treatment modalities.

Editor's Note

Besides the old epidermal-dermal classification of melasma, recent studies show a closer interaction between keratinocytes, melanocytes, and fibrobalasts in pathogenesis of melasma. The confirmed finding of pendulous melanocytes, basement membrane disruption, and increasingly identified contribution of dermal mast cells may yield clearer pathogenesis on further research. While vascular factors are now well-established in the pathogenesis of melasma, the role oxidative stress is emerging and mandates further dedicated research in this area.

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CHAPTER 4

Clinical Features and Classification of Melasma, Wood's Lamp, and Melasma Area Severity Index Score

Nilendu Sarma, Joyeeta Chowdhury, Niharika Jha

INTRODUCTION

Melasma is a common pigmentary disorder. It is a form of acquired hypermelanosis and occurs in sunexposed parts. It develops mostly on the face but occasionally it can also develop on the neck. Rarely, it can also appear on the forearms as well. Melasma is resistant to treatment and often causes significant psychological impact on the patient.

The term "melasma" has been derived from the Greek word "melas" which means black and the term, "chloasma" has been derived from the Greek word, "chloazein" (which implies "to be green"). The term chloasma is often used to describe melasma developing during pregnancy.[1]

Melasma affects all races but is commonly seen in Hispanics and Asians.

It is seen in 0.25–4% of patients in Southeast Asia. It is possibly the most common pigmentary disorder among Indian patients.[2,3] People with darker skin type (i.e. Fitzpatrick type IV, V, and VI) are more prone to develop melasma.

It affects both males and females but is predominantly seen in females. The reported prevalence of melasma in Southeast Asia is 40% of females and 20% of males.[3]

ETIOLOGY

The exact etiopathogenesis of melasma is not known. Genetic predisposition is suggested. About 40% of the affected persons are reported to have at least one relative affected.[4] Factors known to induce or aggravate melasma are discussed here.

Sun Exposure

It is the most important avoidable risk factor. Distribution of melasma exclusively over the sunexposed areas and frequent exacerbation of melasma following prolonged sun exposure are supporting evidence.[1]

Melanocyte proliferation, migration, and melanogenesis are induced by ultraviolet (UV) rays. Ultraviolet rays also stimulate different cytokines like interleukin-1, α-melanocyte stimulating hormone, endothelin-1, and adrenocoticotrophic hormone from the keratinocytes. These potentiate melanogenesis.

Visible light can also cause pigmentation of skin. Pigmentation caused by visible light is more intense and stable. Hence, physical sunscreens should be used to prevent melasma relapses.[5]

Pregnancy

It is known to provoke melasma. Melasma during pregnancy develops in approximately 25% of cases.[6] According to a survey, about 41% of women suffering from melasma developed

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it after pregnancy but before menopause.[7] Some reports suggest fading of pigmentation few months after delivery. However, spontaneous remission might have been over-reported in the past.

Hormone

Hormone therapy in the form of oral contraceptive pills containing estrogen and/or progesterone, intrauterine devices, hormone replacement therapy, and implants may induce or aggravate melasma in about a quarter of affected women.[1]

Melasma has been found to have higher prevalence of hypothyroidism. The implication of this finding is yet to be elucidated.[1]

Cosmetics

Cosmetics especially the perfumed ones and soaps may cause a phototoxic reaction which may trigger melasma. This kind of melasma tends to persist for a long-term.[8,9]

Phototoxic Topical Agents

Melasma may sometimes develop as a phototoxic reaction to certain topical medications.

Drugs

Drugs like phenytoin can also induce melasma like pigmentation. This has been seen in about 10% of patients receiving phenytoin. Pigmentation slowly resolves after the withdrawal of the drug. Phenytoin acts directly on melanocytes causing dispersion of the melanin granules. Increase in pigmentation of the basal epidermis is also seen.[5]

Few cases of imatinib-induced melasma like pigmentation have also been reported.[10]

CLINICAL APPEARANCE

The hyperpigmented light to dark brown or muddy brown patches develop slowly. Patients can have single or multiple lesions. It most commonly appears symmetrically on the face and may occasionally appear on the V area of the neck.

Three clinical patterns of melasma have been recognized depending on the pattern of pigmentation.[7] They are as follows:

1. The "centrofacial pattern": It is the most common pattern (affecting 63% of all cases) and involves forehead, cheeks, upper lip, nose, and chin (Fig. 1).
2. The "malar pattern": It is seen in 21% of the patients. The cheeks and nose are involved in this type (Fig. 2).
3. The "mandibular pattern": It affects 16% of the patients. The ramus of the mandible is involved in this type.

DEPTH OF PIGMENTATION

Four major histological types of melasma have been identified depending upon the depth of pigment deposition (by doing Wood's lamp examination).[5] These are as follows:

Epidermal Type

It is the most common type of melasma depending on the depth of pigmentation. In this type of melasma, pigmentation is intensified under Wood's light. Melanin is increased in all the epidermal layers.

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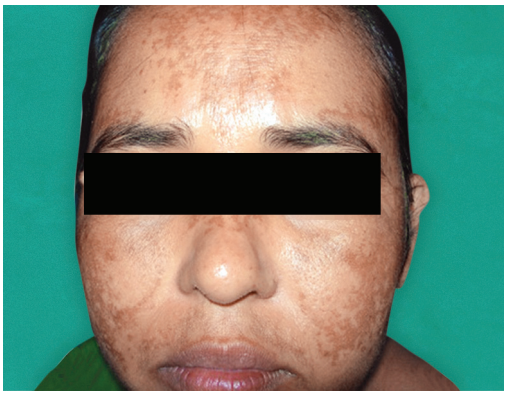

Figure 1: Patient showing brownish nonhomogenous pigmented patches over forehead, nose, malar areas, and upper lip.

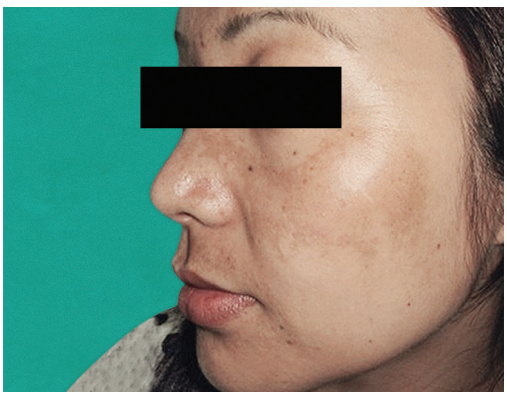

Figure 2: Patient showing diffuse brownish pigmented patches over malar areas and nose.

Dermal Type

In this type, pigmentation is not intensified under Wood's light. In dermal type of melasms, melanophages are distributed throughout the dermis.

Mixed Type

Presence of both the epidermal and dermal patterns noted.

Indeterminate

In dark skinned patients, there is a fourth type, indeterminate as it may not be discernible in dark skin and minimally contributory.

Recent understanding is based on histologic or electron microscopic studies suggest that clear cut distinction in such grouping may not be accurate.

Clinically, the epidermal type is known to have well-defined border, more brown tone, and its response to treatment is much better in comparison to deeper variants. On the other hand, dermal type has ill-defined border.

Dermoscopy can also be used for diagnosing and classifying melasma. It helps in observing the pigment color and its distribution in the various skin layers. It is less affected by the skin type of the patient, vascular and collagen changes, and even by the use of topical preparations. Hence, it is more useful as compared to Wood's lamp.

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The color intensity and the regularity of pigment distribution helps in classifying melasma. For example, when located in stratum corneum, it is dark brown in color and is arranged in a well-defined network. While it presents in shades of light brown and is irregularly arranged when present in the lower layers of epidermis. It spares the hair follicles and also the sweat glands openings. This produces an exaggerated pseudo network pattern with concave borders. This is also known as the "jelly sign."

When the pigmentation is in the dermis, a bluish or a bluish-gray color is seen. Sometimes, the vascular component can be seen.[11]

Reflectance confocal microscopy (RCM) is another noninvasive method of classifying melasma. It can examine skin up to papillary layer of dermis and provides a real-time en face images. Using RCM, melasma can be divided into epidermal and dermal types and it shows complete coherence with histopathology results. In RCM, epidermal melasma appears as hyperrefractile cobblestone cells (hyperpigmented basal cells) and dendritic cells (activated melanocytes). While, the dermal melasma appears as plump bright cells (the melanophages), ragged, less refractile lacy structures (solar elastosis), and dark round to tubulant structures (blood vessels).[5]

DIFFERENTIAL DIAGNOSIS

Several conditions may come into the differential diagnosis of melasma like acquired idiopathic facial pigmentation (zygomatic pigmentation/pigmentary demarcation lines),[12] postinflammatory hyperpigmentation, facial acanthosis nigricans, actinic lichen planus, frictional melanosis, nevus of Ota, acquired bilateral nevus of Ota-like macules (ABNOM) or (Hori's nevus), Riehl's melanosis, peribuccal pigmentation of Brocq, poikiloderma of civatte (POC), and drug-induced pigmentation. Early lesions of melasma appear as small macules and often appear as solar lentigines and ephelides.

MELASMA AREA SEVERITY INDEX SCORING

Melasma area severity index (MASI) score is a formula which is used to calculate the severity of melasma.[13] The face is divided into four regions: forehead, right malar region, left malar region, and chin. Three variables, i.e. total area involved (A), intensity of darkness, (D) and homogeneity of pigmentation (H) are assessed in these four regions and is used to determine the severity of melasma.

A numerical value is assigned for the corresponding percentage area of involvement (A) as follows: 0 = no involvement; 1 = 1–10% involvement; 2 = 10–29% involvement; 3 = 30–49% involvement; 4 = 50–69% involvement; 5 = 70–89% involvement, and 6 = 90–100% involvement.

The intensity of darkness of melasma (D) is determined by comparing the darkness of melasma to the normal skin color. It is graded on a scale of 0–4 where 0 = normal skin color without any hyperpigmentation; 1 = barely visible hyperpigmentation; 2 = mild hyperpigmentation; 3 = moderate hyperpigmentation, and 4 = severe hyperpigmentation.

Homogeneity of hyperpigmentation (H) is again graded on a scale of 0–4 where 0 = normal skin color without any hyperpigmentation; 1 = specks of pigmentation; 2 = small patchy areas of hyperpigmentation measuring less than 1.5 cm in diameter; 3 = patches of hyperpigmentation measuring more than 2 cm in diameter, and 4 = uniform skin pigmentation without any clear areas in between.

Melasma area severity index score is finally calculated by adding the intensity of darkness (D) and homogeneity of pigmentation (H) and the sum of which is multiplied by the numerical value corresponding to percentage of the area of involvement. This value is then multiplied

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by the percentage of the four facial areas, i.e. the forehead, right malar region, left malar region, and chin (10–30%). Thus the formula for calculating MASI score is:

Forehead 0.3 (D + H)A + right malar region 0.3 (D + H)A + left malar region 0.3 (D + H)A + chin 0.1 (D + H)A.

Melasma area severity index score ranges between 0 and 48.

MODIFIED MELASMA AREA SEVERITY INDEX SCORING

Recently, Pandya et al. have devised a modified MASI scoring. They have observed that modified MASI scoring is a reliable scale for measurement of melasma severity.[14] They found out that only the area of involvement and darkness were sufficient for measuring melasma severity. Homogeneity was eliminated and the range of scores were from 0 to 24. The modified MASI score appeared easier to perform.

Modified MASI score = 0.3 A(f) D(f) + 0.3 A(lm) D(lm) + 0.3 A(rm) D(rm) + 0.1 A(c) D(c)

Where A = area of involvement, D = intensity of darkness, f = forehead, lm = left malar region, rm = right malar region, and c = chin

Area of involvement is scored as: 0 = absent, 1 = < 10% involvement, 2 = 10%–29% involvement, 3 = 30%–49% involvement, 4 = 50%–69% involvement, 5 = 70%–89% involvement, and 6 = 90%–100% involvement. Intensity of darkness is graded on a scale of 0 to 4 as: 0 = no pigmentation, 1 = slight pigmentation, 2 = mild pigmentation, 3 = marked pigmentation, and 4 = severe pigmentation.

Editor's Note

Wood's lamp examination is a cheap but not very effective investigative tool for classifying melasma. However, it is easy to perform. Melasma area severity index is a subjective scoring system, as many other investigative tools are not easily available everywhere.

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CHAPTER 5

Investigations in Melasma: Histopathology, Dermatoscopy, and *in vivo* Reflectance Confocal Microscopy in Melasma

Hee Young Kang

HISTOPATHOLOGY

Pigmentation

Histological examinations of melasma have consistently shown that lesional skin is characterized by an increased melanin deposition in the all layers of the epidermis (Fig. 1).[1,2] There was an 83% increase in epidermal pigmentation in lesional skin of 56 Korean melasma patients.[1] Another study showed a 61% increase in epidermal pigmentation in lesional skin in all 11 melasma patients of Fitzpatrick skin type IV to VI.[2] The findings have suggested that there is no true dermal type of melasma.[1,2] Melanophages were present both in melasma lesional and perilesional normal skin in 36% of Korean patients and in all the melasma patients of Fitzpatrick skin type IV to VI.[1,2] There was no statistically significant difference in the amount of dermal melanin in lesional skin compared to that of perilesional normal skin, although there was slight increase in the lesion.[1,2] The dermal melanophages are commonly found in the sun-exposed skin and the normal facial skin has pigments in the dermis. Therefore, regarding the pigmentation level, melasma is characterized by epidermal hyperpigmentation with or without melanophages.

Melanocytes

The number of melanocytes in melasma is normal or slightly increased. NKI/beteb immunostaining showed an increase in the number of melanocytes, while Mel-5 or MITF

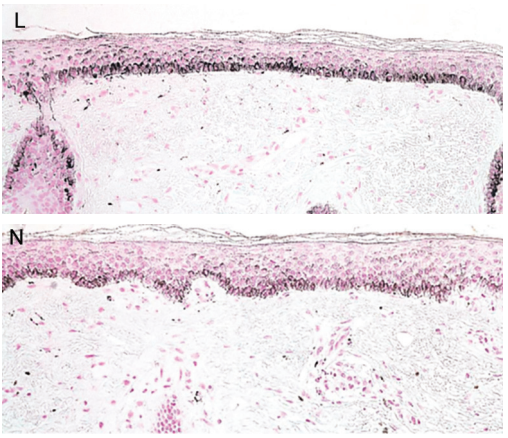

Figure 1: Increased epidermal pigmentation in melasma. Fontana-Masson staining shows more pronounced epidermal hyperpigmentation in lesion (L) compared to perilesional normal skin (N). It is noticed that there are a few melanophages in the dermis of the lesional skin (L) and also in the perilesional normal skin (N).

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staining did not confirm this finding.[1,2] The melanocytes within the lesional skin are larger, intensely stained with prominent dendrites and contain more melanosomes, suggesting that the cells are active. There was an up-regulation of many melanogenesis-related genes such as *tyrosinase*, *TYRP1*, *TYRP2,* and *MITF* in lesional skin compared to perilesional normal skin. An interesting feature observed on histopathology is the melanocytes protruding into the dermis, so called pendulous melanocytes.[3-5] The protruding cells were observed in half of melasma specimens.[3] These cells hung down from the basement membrane and it was suggested that the loosening of basement membrane is related to the pendulous change of the melanocytes.[4,5] On the reflectance confocal microscopy (RCM) images, these cells were appeared as dendritic cells, in which the morphology suggests hyperactivity of the cells.[6] However, the pendulous melanocytes are not pathognomonic for melasma and also observed in other hyperpigmentary disorders such as solar lentigines and even in normal black skin.

Basement Membrane

The basement membrane structure in melasma lesional skin is not intact and looks disrupted.[4,5] The overall type IV collagen expression was significantly reduced in lesional skin compared to perilesional normal skin.[4] The feature was more evident at the margin of pendulous melanocytes. It was suggested that chronic UV irradiation is responsible for the loosening of basement membrane through up-regulation of MMP2 expression in melasma.[4] The change in the basement membrane was suggested to be related to facilitate the interaction between factors secreted from the dermis and epidermal melanocytes to develop melasma. Recently, it was shown that Cadherin-11 could induce basement membrane disruption and dermal changes in melasma.[7]

Dermal Changes

Melasma has alteration in dermal structures in addition to pigmentation changes, suggesting role of dermis for melasma development.[6-11] Increased solar elastosis in lesional skin and increased mast cells localized to elastotic area in melasma have been shown.[6] Overexpression of both stem cell factor (SCF) from fibroblast and increased number of fibroblast have been found in melasma.[8] Increased expressions of keratinocyte growth factor (KGF) and secreted frizzled-related protein 2 (sFRP2) secreted from fibroblasts were also observed in melasma.[9,10] It was shown that the fibroblasts from the melasma lesion and perilesional skin secreted more nerve growth factor (NGF)-β than those in normal buttock skin.[11]

Melasma lesions have more vascularization as compared to the perilesional normal skin.[12] The number of vessels had a positive relationship with epidermal pigmentation in melasma lesional skin. Increased expression of vascular endothelial growth factor (VEGF) in keratinocytes was suggested as the major angiogenic factor for altered vessels in melasma. These all findings have suggested that during sun exposure, network of cellular interactions between keratinocytes, fibroblasts, and perhaps vasculature and melanocytes may play an important role in the development of epidermal hyperpigmentation in melasma.

DERMATOSCOPY AND *IN VIVO* REFLECTANCE CONFOCAL MICROSCOPY

Dermatoscopic examination of melasma revealed irregular pigmentation with a fine brown reticular pattern and capillary vessels in some parts of the lesions. A study has suggested that dermatoscopic examination did not help in differentiating the type of melasma.[13] However, broadly it is a good tool to differentiate epidermal, dermal, and mixed patterns.

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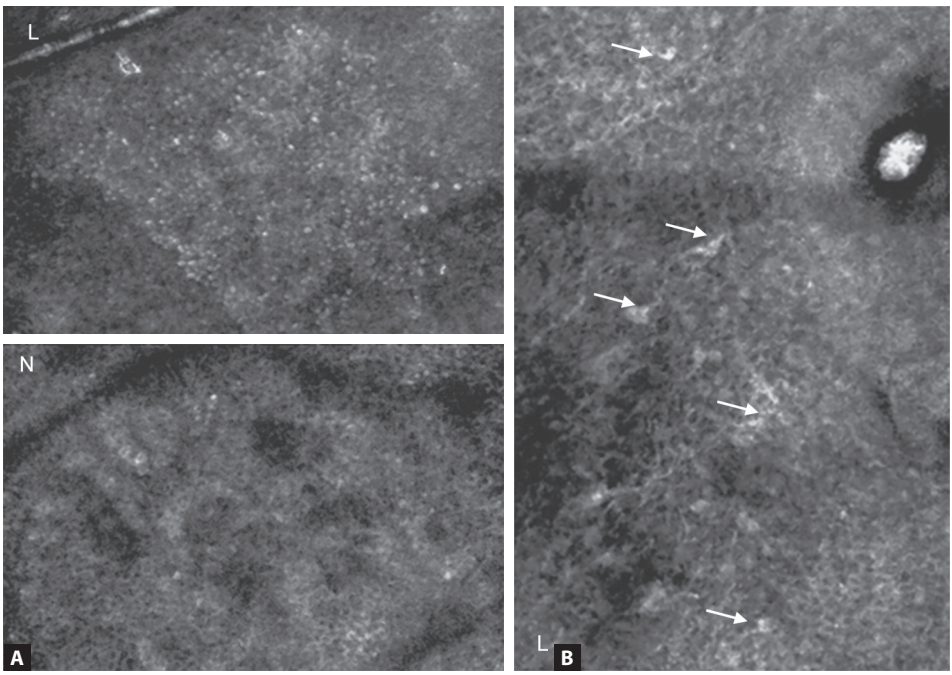
In vivo (RCM) images of melasma showed characteristic significantly increased hyperrefractile cobblestone pattern at the level of basal cell layer in lesional skin compared to perilesional normal skin supporting the existence of epidermal hyperpigmentation in all melasma lesional skin (Fig. 2A).[5] Melanophages were recognized in melasma skin in 34.5% of patients and also in the control adjacent skin of four of these patients but to a lesser extent. Most melasma skin showed an abrupt transition from stratum spinosum to papillary dermis and moderately refractile lacy structures (solar elastosis) in the dermis, suggesting the existence of chronic solar damage in the melasma. These all findings are in agreement with available reports regarding histological changes in melasma. A new finding through noninvasive property of RCM is that the distribution of melanophages in melasma is not homogeneous.[5] The distribution of melanophages is very heterogeneous because it can vary from one melasma region to another and even inside a given melasma region.

Another new finding of RCM images of melasma, has detected hyperactivated melanocytes in some patients (6/25 patients) of melasma (Fig. 2B).[5] On the RCM images, the cells were shown as bright dendritic cells at the level of the dermoepidermal junction in melasma. Immunohistochemical studies have confirmed that these cells correspond to melanocytes, not Langerhans cells. Interestingly, recent study has suggested that the cases showing the presence of these dendritic cells had an early relapse of melasma after treatment.[9] It was also shown that the pigmentary lesion of melasma is rather heterogeneous and in heavily pigmented areas, the dendrites of melanocytes are frequently observed around the basal layer.[10]

The noninvasive nature of this technique suggests that RCM is a suitable tool for treatment monitoring.[14-16] In parallel to the clinical improvement, it was noted a statistically significant decrease in pigmented cells on RCM images after treatment.[13] Interestingly,



Figures 2A and B: Reflectance confocal microscopy images of melasma. **A,** Increased cobblestoning and loss of dermal papillary rings at the basal layer in lesion (L) compared to perilesional normal skin (N); **B,** Dendritic cells (arrowheads) at the level of dermoepidermal junction of the lesional skin (L).

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the cases showing presence of dendritic cells had an early relapse of melasma after laser toning treatment.[13] This clinical outcome further supported the hypothesis that these cells correspond to activated melanocytes and open the question whether the laser treatment should be stopped or differently modulated in these cases.

Editor's Note

Reflectance confocal microscopy is a noninvasive investigation for melasma and is suitable for monitoring the treatment as opposed to histopathology and dermoscopy alone.

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CHAPTER 6

Investigations in Melasma: Dermoscopy in Melasma

Saloni Katoch

INTRODUCTION

Melasma is a common acquired hyperpigmentary disorder occurring mainly on sunexposed skin on the face and is often a cause of social stigma and embarrassment. Dermoscopy in melasma is an evolving domain with some dermoscopic patterns being consistent with this disorder. It not only aids in early identification of subtle cases but also in differentiating melasma from other facial hyperpigmentary conditions, thereby reducing the need for a facial biopsy. Monitoring treatment efficacy and detection of complications is another utility of this noninvasive tool.

On dermoscopic examination of melasma the following can be appreciated.

PATTERN

Reticular pattern is the global feature seen in all melasma lesions. This can be superimposed by blotches, globules, and granules. Sparing of sweat gland and follicular openings produce the pseudo network pattern with concave borders referred to as the "jelly sign"[1] (Fig. 1).

COLOR

The color of melanin is observed accurately depending upon the amount of pigment, depth, and location; going from black when localized in the stratum corneum, shades of brown in the lower layers to blue or bluish-gray in the dermis[2] (Figs 2 and 3).

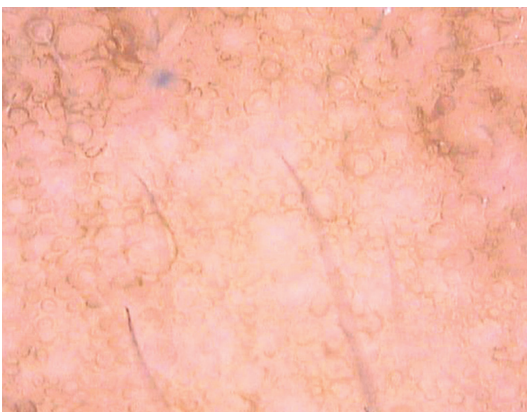

Figure 1: Reticuloglobular brown pigmentation (epidermal melasma).

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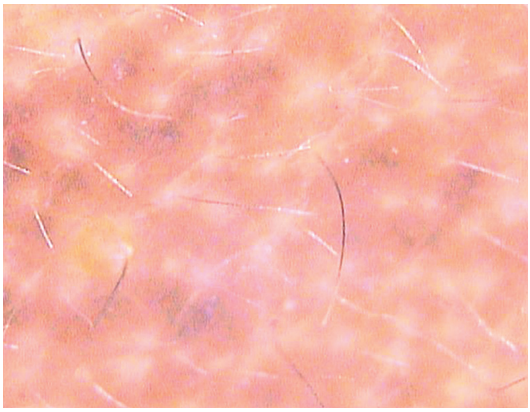

Figure 2: Blue-gray pigmentation (dermal melasma).

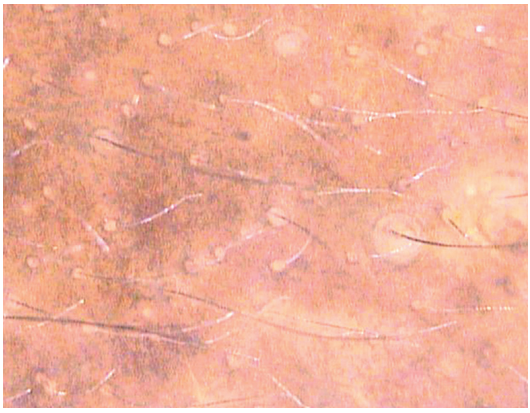

Figure 3: Gray-brown pigmentation (mixed melasma).

OTHERS

- Dermoscopy can aid in detecting complications arising due to topical medications like atrophy, telangiectasia, depigmentation, exogenous ochronosis, and steroid dermatitis (Figs 4 and 5)
- Telengeictasia: The presence of these fixed dilated vessels could indicate prior treatment, steroid abuse, or an underlying erythematotelangeictatic rosacea.[4] Recent research has also demonstrated an increase in the number and size of dermal blood vessels in the lesional skin suggesting an interaction between the changed vasculature and the melanocytes, thereby supporting the vascular theory in the pathogenesis of melasma[4,5] (Fig. 5)
- Exogenous ochronosis: Patients presenting with a history of prolonged hydroquinone usage, unresponsiveness to treatment, and worsening of pigmentation, following use of skin lightening agents should be screened. Skin biopsy continues to remain the gold standard for diagnosis but dermoscopy aids in early detection, differentiation from melasma, and as a guide for therapy in such patients.[6] The clinical and dermoscopic features of exogenous ochronosis are listed in table 1[6,7] (Figs 6 to 8).

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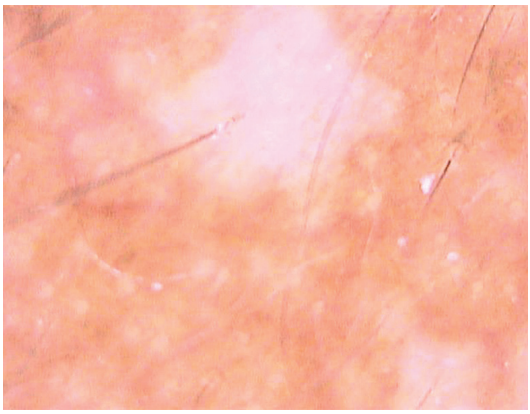

Figure 4: Posttreatment depigmentation.

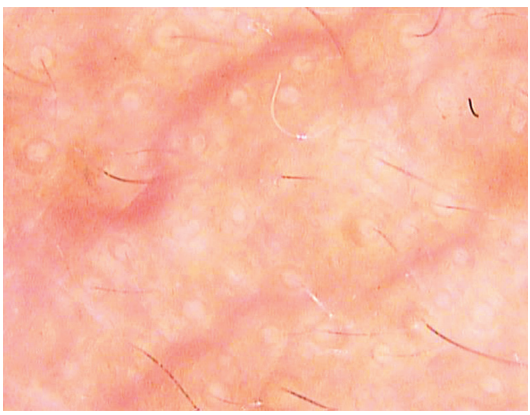

Figure 5: Telangiectasia with areas of pigment clearance.

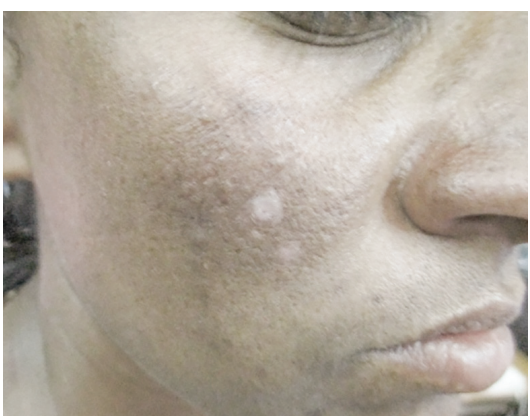

Figure 6: Gray-brown macules with interspersed "confetti-like" depigmented areas over a background of diffuse brown hyperpigmentation.

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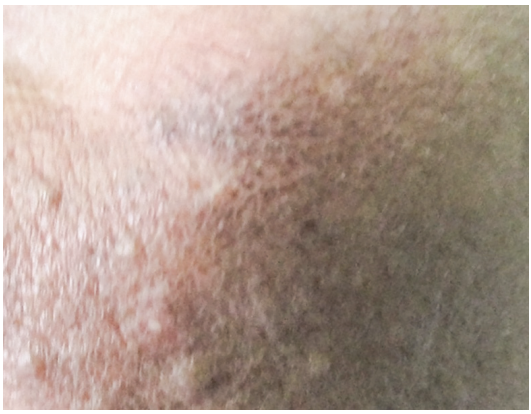

Figure 7: "Caviar-like" blue-gray pinpoint papules (arrow) with underlying erythema, speckled hyperpigmentation, and papular eruptions.

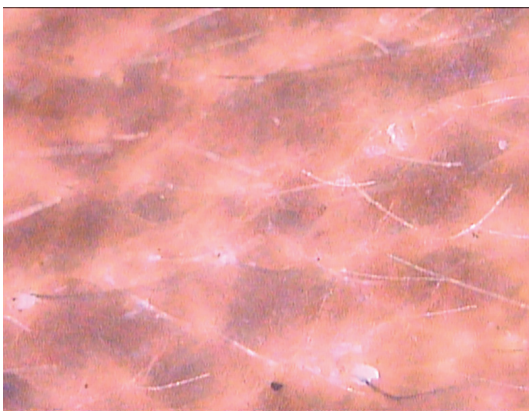

Figure 8: Gray-blue amorphous structures obliterating some follicular openings (exogenous ochronosis).

Table 1: Clinical and dermoscopic features of exogenous ochronosis

Clinical presentation	Dermoscopic features
• Symmetric hyperpigmentation with gray-brown or blue-gray macules with a "sooty appearance" • Pinpoint "caviar-like" hyperchromic papules • Scanty atrophy and papulonodular lesions in the later stages	• Gray-brown to blue-gray amorphous structures obliterating some follicular openings on a diffuse brown background • Gil et al. reported the dermoscopic features of exogenous ochronosis as irregular, brown-gray, globular, annular, and arciform structures[8]

In a comparative study between dermoscopy and Wood's lamp in classification of melasma, the authors considered that the former is more applicable, more appropriate, and helpful for routine diagnosis, assessment, and monitoring of patients with melasma. Dermoscopic examination allows an objective classification of melasma based on the color of pigment observed. Epidermal type being brownish with a regular pigmented network; dermal type with shades of bluish-gray, the network losing regularity; and the mixed type with features compatible with both.[2]

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Dermoscopic evaluation is important for an improved diagnosis of the melasma type, differentiating it from other facial hyperpigmentary conditions, prognosis, and for monitoring treatment efficacy with a potential to detect complications thereby improving the management of our patients.

ACKNOWLEDGMENTS

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Editor's Note

Dermoscopy is an evolving science and may help to pick up epidermal, dermal, and mixed melasma as well as various complications of treatment. It is one more useful tool available to the dermatologist.

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CHAPTER 7

Photoprotection for Melasma

Narendra Gokhale

ELECTROMAGNETIC RADIATION

The energy from the sun reaches us in the form of electromagnetic waves (Table 1).[1]

Table 1: Spectrum of electromagnetic radiation

Wave length	200–290 nm	290–320 nm	320–340 nm	340–400 nm	400–700 nm	700 nm–1 mm
Name	UVC	UVB	UVA2	UVA1	Visible	Infrared (IR)

UVA, ultraviolet A; UVB, ultraviolet B; UVC, ultraviolet C.

PIGMENTATION FOLLOWING ULTRAVIOLET EXPOSURE

Pigment production occurs in skin following both ultraviolet A (UVA) and ultraviolet (UVB) exposure (Tables 2 and 3).

Table 2: Effect of different ultraviolet wavelengths on skin[2-4]

Type	**Effect**
Ultraviolet B	• Absorbed by DNA and proteins • Direct damage • Sunburn • Cancer
Ultraviolet A	• Not absorbed by DNA • Penetrates deeper • Aging • Tanning • Immunosuppression • Photocarcinogen • Exogenous photodermatitis • Idiopathic photodermatoses

DNA, deoxyribonucleic acid.

Table 3: Time dependent effects of ultraviolet radiation on skin

Immediate	**Delayed**
• Sunburn—UVB • Tanning—UVB • Vitamin D synthesis • Thickening	• Tanning—UVA • Aging—UVA • Malignancy UVB • Immunological changes

UVB, ultraviolet B, UVA, ultraviolet A.

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Ultraviolet A induces three types of pigmentation:

1. Immediate pigment darkening (IPD) develops rapidly in minutes and it also fades rapidly
2. Persistent pigment darkening (PPD) develops in few hours and may persist for many weeks depending on the UVA dose and the skin type
3. Delayed pigmentation starts after some days and is long lasting. It is due to increased melanin synthesis.[4]

Ultraviolet B induced tanning is a delayed pigmentation due to melanin synthesis, usually following a burn and disappears with epidermal turnover.

In darker skinned individuals, UVA has greater pigmenting effects than UVB.[5]

Role of Infrared Radiation

In the last few years, interest has built up about the role of infrared (IR) radiation which was hitherto considered innocuous. Infrared has been shown to potentiate the effect of UV radiation and cause damage to elastin fibers.[6]

PHOTOPROTECTION

General measures for photoprotection are given in box 1.

BOX 1 General measures[3]

- Avoid sun throughout the day
- Wear broad hats and scarves whenever going out
- Keep to the shade when outside
- Avoid scented cosmetics and wet wipes

SUNSCREENS

Sunscreens are over-the-counter drugs which are applied with the intention to prevent sunlight to reach skin.[2,3,7,8] Words such as sunblock are not acceptable (Box 2).

BOX 2 The ideal sunscreen

- Broad spectrum (covers UVB + UVA II + UVA I)
- Photostable
- Good substantivity
- Cosmetically acceptable
- Water resistant
- Non-sensitizing
- Fragrance free
- Cost effective

UVB, ultraviolet B; UVA, ultraviolet A.

Classification of Ingredients

Sunscreens are divided into organic and inorganic depending on the mechanism of action.[9-11] The terms physical and chemical are no longer used. There are three commonly used nomenclatures for sunscreen agents in the world. These are the International Nomenclature Cosmetic Ingredient (INCI) name, US adopted name (USAN), and trade name.[11]

Inorganic Sunscreens

These act by reflecting and scattering UVR. Inorganic sunscreens are excellent for heavy exposure as well as melasma, as they act on UV, visible, and infrared spectrums and are opaque, providing a good camouflage effect. However, these are messy, comedogenic,

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and these are concerns with regarding free radical production. To prevent free radical production and whiteness, they are being formulated in micronized forms coated with dimethicone or silica.

Zinc oxide has greater protection in the UVA1 range. Micronized titanium dioxide shows synergistic effects with organic filters. Iron oxide containing creams give good protection from visible light as well, which is important for melasma patients. Visible light protecting sunscreens with inorganic sunscreens including titanium dioxide, zinc oxide, and iron oxide had a beneficial effect on 4% hydroquinone in melasma compared to UV only sunscreen (SPF 50+ for both) in a comparative study in 68 Mexican patients (Box 3).[12]

BOX 3 Inorganic sunscreens

- Zinc oxide
- Titanium oxide
- Magnesium oxide
- Iron oxide
- Red veterinary petrolatum

Organic Sunscreens

These are aromatic compounds with a carboxyl group that absorb UV light of a specific wavelength, and then emit a longer wavelength of lesser energy, usually in the form of insensible heat.[3,8,9,11] The molecule may structurally degrade because of the high energy state when it is labeled as photounstable (Table 4).[10]

There is a risk of contact dermatitis especially with benzophenones and PABA. Avobenzone and cinnamates are photounstable, and hence are combined with octocrylene and tinosorb S. Synergistic effect is shown by the combination of TDSA and DTS, and TDSA and BEMT (Table 5).[11]

Table 4: Organic ultraviolet B filters

US adopted name	International Nomenclature Cosmetic Ingredient name	Peak absorption wavelength (nm)
Aminobenzoates		
PABA	PABA	283
Padimate O	Ethylhexyl dimethyl PABA	311
Cinnamates		
Octinoxate	Ethylhexyl methoxycinnamate	311
Cinoxate	Cinoxate	289
Salicylates		
Octisalate	Ethylhexyl salicylate	307
Homosalate	Homosalate	306
Trolamine salicylate	Time and extend application salicylate	260, 355
Benzophenones		
Others		
Octocrlene	Octocrylene	303
Ensulizole	Phenylbenzimidazole sulfonic acid	310
Mexoryl XL	Drometrizole trisiloxane	303, 344

PABA, para-aminobenzoic acid.

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Table 5: Organic ultraviolet A filters

Class	Name	Peak absorption wavelength (nm)
Benzophenones		
Oxybenzone	Benzophenone 3	288, 325
Sulisobenzone	Benzophenone 4	366
Dioxybenzone	Benzophenone 8	352
Tinosorb M	MBBT	305, 306
Tinosorb S	BEMT	310, 343
Others		
Methylanthranilate	Meradimate	355
Avobenzone/Parsol 1789	BMDM	360
Mexoryl SX	TDSA	345
Mexoryl XL	DTS	303, 344
Uvinul A+	DHHB	354
NeoHeliopan AP	DPDT	335

BMDM, butyl methoxydibenzoylmethane; BMET, bis-ethylhexyloxyphenol methoxyphenyl triazine; DHHB, diethylamino hydroxybenzoyl hexyl benzoate; DPDT, disodium phenyl dibenzimidazole tetrasulfonat; DTS, drometrizole trisiloxane; MBBT, methylene bis-benzotriazolyl tetramethylbutylphenol; TDSA, terephthalylidene dicamphor sulfonic acid.

INFRARED PROTECTION

Polygonum aviculare as a 2% cream has been shown to reduce the oxidative stress caused by infrared radiation.[13]

Sunscreen Protection Criteria

There is much confusion and ignorance about judging the efficacy of sunscreens (Box 4).

BOX 4 Criteria for evaluation of sunscreen protection

- Sunburn protection factor
- Protection grade of UVA factor Japanese standard
- Australian/New Zealand standard
- European Union rating
- Boots star rating
- Critical wavelength

Sunburn Protection Factor

It is defined as the ratio of the least amount of ultraviolet energy (UVB) required to produce minimal erythema on sunscreen protected skin to the amount of energy required to produce the same erythema on unprotected skin. About, 2 mg/cm^2 layer of sunscreen is required to call the skin protected.[2-4,6-8,14]

With chronic exposure, the damage caused by UV radiation is halved by a sunscreen having SPF30 compared to a sunscreen of SPF15.[2-4,8,9,11]

Products having SPF >50 can only write SPF 50+.

PA Rating[15]

It is the ratio of the UVA dose required to produce PPD after 2–24 hours of exposure on protected skin, to the UVA dose required to produce the same effect on unprotected skin. Since it measures the ability to prevent tanning, it is a more useful measure for darker skin types and patients of melasma (Table 6).

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Table 6: PA rating according to the degree of persistent pigment darkening ratio	
PA	PPD ratio
+	2–4
+ +	4–8
+ + +	>8

Australia New Zealand Standard

This is an *in vitro* method. An 8 µm layer of the product should not transmit more than 10% of the radiation and a 20 µm layer should not transmit more than 1% of the radiation of wavelength 320–360 nm.

European Standard

It states that SPF/UVAPF ratio should be ≤3.[16]

Boots Star Rating

This is an *in vitro* method which is a measure of UVA protection where UVA to UVB absorbance before and after irradiation is calculated as shown in table 7.

Table 7: Boots star rating		
Before	After	Boots star rating
<0.6	<0.56	None
>0.6	>57	***
>0.8	>76	****
>0.9	>86	*****

Substantivity

Substantivity refers to the ability of a sunscreen to retain its effectiveness under the stress of exercise, sweating, and swimming.[3,8]

A sunscreen is labeled as water resistant if it is able to retain its efficacy after two sequential immersions in water for 20 minutes each. A very high water resistant sunscreen can do so after four sequential immersions. A water resistant sunscreen is also sweat resistant. The word waterproof is not to be used.

Application of Sunscreens

A thick layer ideally 2 mg/cm^2 should be applied for the sunscreen to be effective (Table 8).[3,9,17]

Table 8: The teaspoon rule	
3 mL or just more than half teaspoon	Each arm, face, and neck
5 mL or just more than one teaspoon	Each leg, chest, back

Selecting the Right Sunscreen for a Patient with Melasma

The following points should be considered:

- Inorganic sunscreens are preferred as they have a broad spectrum covering UVA, UVB as visible spectrum, and also provided camouflage effect as these are opaque[15-16]
- Since inorganic alone are not cosmetically acceptable, blend with organic

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- Use liberally and repeatedly even when they are indoors
- Note the coexistent conditions like acne, occupation, and the needs and aspirations of the patient. Use a gel based preparation for acne patients, outdoor workers, and water in oil emulsion for aged and dry skin.

COSMETIC CAMOUFLAGE FOR MELASMA

Cosmetic camouflage is a make-up used to conceal the skin discoloration and normalize the appearance of skin helping in improving self-esteem and quality of life. These products are different from foundations as they have 25% more pigment and also have fillers with optical properties.[18] Indications vary from macular lesions to papules, nodules, scars, injuries, etc. (Boxes 5–8).

BOX 5 Goals of cosmetic camouflage

- Match all skin tones and blend into the surrounding area
- Conceal adequately
- Water and sweat resistant
- Not slide off
- Stay for a sufficient time
- Be easy to apply

BOX 6 Types of cosmetic camouflage

- Full concealment
- Pigment blending
- Subtle coverage

BOX 7 Steps of cosmetic camouflage

- Ask the patient about previous experience
- Cleanse, exfoliate, and moisturize the area preferably with a sunscreen
- Match the product with patient's skin
- Identify underlying skin tones that are contributing to the skin color, e.g., hemoglobin—red, keratin—yellow, melanin—brown
- Understand color coordinates –hue*, value,† and intensity‡

*Hue is the coordinate for the spectrum color, commonly the color name.
†Value is the relative darkness or lightness.
‡Intensity or chroma or saturation is the brightness.

BOX 8 Key points

- Difficult to match with a single color, so mix and match
- Watch out for manufacturer variation
- Judge on the skin, not in the container
- Different areas of the body may vary in color
- Keep tester kit
- Provide a mirror to the patient
- Photograph before and after
- Testing area should be well illuminated

CONCLUSION

Photoprotection forms the cornerstone of any therapeutic regimen for melasma and increases the effectiveness of other therapeutic modalities. It helps in preventing synthesis of new melanin by melanocytes and helps in improving the overall texture of the skin. Physicians should be aware of the various options available to them and choose a product wisely.

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Editor's Note

Photoprotection, if used effectively, could play an important role in treatment of melasma. Visible light has a role to play in melasma, hence inorganic sunscreens are important. Cosmetic camouflage can improve the quality of life in patients with melasma.

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CHAPTER 8

Hydroquinone Based Therapies for Melasma

Rashmi Sarkar, Shivani Bansal, Sumit Sethi

INTRODUCTION

Melasma is derived from the Greek word, "*melas*" meaning black. It is an acquired pigmentary disorder manifesting as symmetric, light to dark brown colored patches on face. The border of these patches can be geographic, serrated, and irregular. Although melasma can occur in all skin types and ethnicities, it is particularly common in Fitzpatrick skin types IV to VI. It is more common in female with first manifestation, especially after pregnancy. However, it was seen that men are affected in 10% of melasma. Out of all patients of melasma in an Indian study, 20.5% were men and no difference was noted clinically and histopathologically, compared to melasma in females.[1]

Multiple risk factors and biological/environmental triggers have been proposed in the etiopathogenesis of melasma, including female sex, genetics, degree of exposure to solar radiation, pregnancy, oral contraceptives, hormonal therapies (e.g., estrogen-progesterone treatments), and photosensitizing medications. There are three types of melasma according to patterns of distribution which are: (i) centrofacial (65% of cases), (ii) malar (20% of cases), and (iii) mandibular (15% of cases). Histologically, the condition may be primarily epidermal, dermal, or mixed. In epidermal melasma, excess melanin deposition is present in basal, suprabasal, and stratum corneum layers, whereas dermal melasma manifest melanophages in both the superficial and the deep dermis.

The management of melasma remains a challenge. Topical therapy is playing main role of treatment. Different therapeutic modalities, especially the gold standard hydroquinone (HQ) have been used in the topical treatment of melasma. The other modalities which are used are topical depigmenting agents, used alone, or in combinations and peeling agents like glycolic, trichloroacetic acid, salicylic, and lactic acid. Limited success was seen with physical agents like lasers and dermabrasion.[2] All patients should be instructed to use, broad-spectrum, high sun protection factor (SPF) sunscreens. Although clinical studies on role of sunscreens are lacking.

This chapter focuses on HQ therapy in melasma, which could potentially be used as alone or in combination in treatment for melasma.

HYDROQUINONE

Hydroquinone is a hydroxyphenolic compound. Its structure show homology to precursors of melanin. It inhibits the enzyme tyrosinase, which is causing conversion of DOPA to melanin. It also acts by degradation of melanosomes, destruction of melanocytes, and inhibiting deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis.[3] As concentration of HQ increases, its efficacy also increases. However, at the same, incidence of adverse effects also increases. Hydroquinone is available as cream form or as an alcohol-based solution.

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As it rapidly oxidizes on exposure to environment, it is very difficult to formulate hydroquinone in a stable form. Typically, HQ skin-lightening creams changes to a darker yellow or brown upon oxidation from creamy color. With discoloration, the effectiveness of the HQ also decreases. Products with any color change should be discarded.

Hydroquinone is the most frequently used compound in melasma and it is considered as the gold standard therapy, particularly of the epidermal type of melasma. Most of the patients treated with HQ had shown variably good yet reversible results. After 5–6 weeks, its depigmenting effects start becoming evident. Treatment should be continued for minimum of 3 months, up to 1 year. Hydroquinone can also be combined with other agents like topical steroids, retinoids, kojic acid (KA), and glycolic acids (GAs).

MONOTHERAPY

It is used as monotherapy in concentrations of 2–5%, though 4% is the preferred one especially in the Indian setup. In a double-blind placebo-controlled trial in melasma by Ennes et al., both HQ 4% and placebo were applied twice daily till 12 weeks in 48 patients. Melasma in 40% of patients treated with HQ showed total improvement and there was no treatment failures. In contrast, only 10% of patients had total improvement in the placebo group, but treatment failures occurred in 20% of patients.[4]

COMBINATIONS

Hydroquinone can be combined with steroid and retinoids as triple combination therapy or can also be used along with chemical peels.

RETINOID WITH HYDROQUINONE

Retinoids, such as tretinoin, has an inhibitory effect on tyrosinase. It interrupts melanin synthesis by inhibiting the enzyme's transcription and dopachrome conversion factor. It also reduces hyperpigmentation through the mechanism of desquamation.[5] Compared to HQ, the clinical improvement with retinoid are visible at least 24 weeks with retinoid. Retinoid acid (RA) can be used in concentrations ranging from 0.05 to 0.1%. In a 20-week open label study, a combination of RA 0.1% plus 3% HQ has been tried in 40 Korean women. Excellent to good improvement were seen in 59% of patients after therapy in both physician and patient evaluation. Mild to moderate reactions to tretinoin cream were seen in majority of patients (96%). But on continuation of therapy, reactions like burning, itching, erythema, and scaliness were decreased.[6]

Glycolic Acid with Hydroquinone

Glycolic acid 5–20% is an α-hydroxy acid. It can be combined with hydroquinone to increase its efficacy. It is an exfoliative agent. It causes thinning of the stratum corneum, exfoliate melanin in the basal layer of the epidermis, and also increases collagen synthesis in the dermis. All these effects lead to decrease in pigmentation.

In a randomized controlled trial, a cream containing 10% GA plus 4% HQ in combination with vitamins C and E and sunscreen was compared with a cream containing sunscreen alone in group of Hispanic patients. A significant decrease in the pigmentation was seen in group of patients using the study cream compared with sunscreen alone; ($p = 0.001$). Many patients complained of irritation as a side effect which was temporary. It resolved on discontinuation of application of study cream for sometime and application of moisturizers.[7]

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Kojic Acid and Hydroquinone

Kojic acid 2% is produced by the fungus *Aspergillus oryzae*. It also inhibits the tyrosinase enzyme and is also a potent antioxidant. Kojic acid may be used as a first-line application if a patient is not tolerating other therapies. It is used concentrations ranging from 1 to 4% and has been found equivalent to other therapies. However, side effect like irritation is more commonly seen in it. In a study, KA in combination with HQ 2% was seen as superior depigmenting agent as compared to KA alone or with its combinations with 0.1% betamethasone valerate or a combination of 0.1% betamethasone valerate and HQ 2%.[8]

Triple Combination Therapy

The preferred topical application is in the form of triple combination (TC) where HQ is used along with a topical steroid and a retinoid. The addition of tretinoin in TC therapy decreases pigmentation by causing exfoliation and preventing the oxidation and improving the epidermal penetration of HQ. On addition of topical corticosteroids, the irritant effects of hypopigmenting agents decreases, and it also inhibits melanin synthesis by decreasing cellular metabolism. Kligman formula (KF) is most commonly used agent in melasma. It was first introduced in 1975 as a combination of HQ 5%, tretinoin 0.1%, and dexamethasone 0.1%. From the years, KF has been extensively studied in various different combinations to increase its efficacy and by decreasing its side effects.[9]

In a multicenter, randomized, investigator-blind study in 641 adult patients of moderate to severe melasma done by Taylor et al., efficacy of TC cream containing tretinoin 0.05%, hydroquinone 4.0%, and fluocinolone acetonide 0.01% (RA + HQ + FA) were compared with the combination agents tretinoin plus hydroquinone (RA + HQ), tretinoin plus fluocinolone acetonide (RA + FA), and hydroquinone plus fluocinolone acetonide (HQ + FA) in Fitzpatrick skin types I–IV.[10] It was seen at the end of week 8 ($p < 0.0001$) that significantly more patients treated with triple combination (26.1%) showed excellent improvement compared with the other treatment groups (4.6%). More than 70% of patients treated with triple combination showed 75% reduction in pigmentation as compared with only 30% in patients treated in other groups.

Among the medical therapies analyzed by a recent Cochrane review, TC creams have been found to be the best topical therapy.[11] In a recent multicenter trial by Chan et al., 260 South East Asian patients were randomized to TC (FA 0.01%, HQ 4%, RA 0.05%) cream or 4% HQ cream for 8 weeks. More patients in the TC group (87/125) compared to the 4% HQ group (57/129) achieved a score of 0 (clear) or 1 (minor hyperpigmentation) which was significant.[12] A similar study on 120 patients demonstrated significantly more improvement in the triple combination groups than in the HQ group.[13]

The adverse events associated with triple combination cream are low. In a long-term, multicenter, open-label, study in 173 patients of once-daily application of TC therapy (FA 0.01%, HQ 4%, RA 0.05%), no cases of skin atrophy were observed after 6–12 months of treatment (one or two course). Only six cases showed telangiectasia, which later on improved by the end of the study. Application-site reactions were most adverse effects seen, which were mild and transient in nature and resolve without any therapy.[14] In an another study of 62 patients with moderate to severe melasma, serial histopathologic examination of skin biopsies were done to see the atrophogenic potential of same TC cream for 24 weeks. There were no significant histopathologic signs of atrophy of the skin at any time point throughout the study.[15] To maintain safety profile, TC creams can be used continuously for 12 weeks then can be maintained twice per week for another 12 weeks if no relapse occurs.[16]

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Triple combination creams can be used in combination with chemical peels or used as priming agents before chemical peels. In an Indian study, 40 patients with Fitzpatrick skin types III–IV with moderate to severe melasma were randomized to treatment with the modified Kligman's formula (hydrocortisone 1%, HQ 2%, tretinoin 0.05%) daily plus six serial GA 30–40% (chemical peel) sessions at intervals of 3 weeks or to modified KF alone.[17] Compared with baseline, a significant decrease in the melasma area and severity index (MASI) score at 21 weeks was noted in both groups. But the group having GA peel also showed more rapid and greater improvements than the other group.

Hydroquinone and Vitamin C

Although there is no study determining the stability and efficacy of vitamin C with hydroquinone, but still there are serum, gel preparations in the market which has hydroquinone and vitamin C in combination. These products are promoted to have good efficacy.

Others

A recent study in 15 Latin American women incorporated hyaluronic acid with HQ and GA in the treatment of melasma as a novel cream preparation. At the end of study, this combination was found it to be well tolerated and with a significant decrease in MASI scores.[18] In an another study in 20 patients of mild to moderate melasma, cream formula containing 4% hydroquinone + 10% glycolic acid + 0.01% hyaluronic acid was very effective with no major side effects.[19]

ADVERSE REACTIONS

Adverse reactions of HQ are directly linked to concentration used and the duration of given treatment. Most common side effect seen is irritation. Adverse effects like erythema, burning, colloid milium, irritant and allergic contact dermatitis, nail discoloration and transient hypochromia are also common. Prolonged use of HQ can lead to blue black pigmentation of treated areas known as ochronosis. There was a proposed ban on HQ in 2006 due to concerns of ochronosis and carcinogenicity, but subsequently it was observed that the evidence of carcinogenicity due to topical application in human beings was not substantial. There is no pregnancy warning label in majority of over the counter (OTC) dermatologic products containing hydroquinone.

Monobenzyl ether, or any other ethers of HQ, can lead to a permanent loss of melanocytes with the formation of a confetti-like leukoderma. Hence, their use is discouraged. Very few complications were noted in short-term continuous therapy with long-term "weekend only" or "three times weekly" maintenance therapy but associated with good benefit for treating both melasma and postinflammatory hyperpigmentation.

Hydroquinone and Controversy

There are several important health issues which should be known before considering the safety of HQ. It is known to cause ochronosis. It is not known that this is a result of the effect of HQ alone or with combination with other substances present in the formulation. Oral HQ was seen to cause cancer in rodents if they are fed with large amounts, yet human carcinogenicity has not been established. Although there is minimal absorption in topical application, HQ remains controversial. It is a strong oxidant which gets rapidly converted to

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the products p-benzoquinone and hydroxybenzoquinone, which are toxic to melanocytes. These by-products may cause depigmentation.[20]

Regulatory agencies in Japan, Europe, and most recently the United States of America, have raised alarms regarding the safety of HQ. In some countries, the use of HQ has been banned in cosmetic preparations and OTC products. However, despite 40–50 years use of hydroquinone for medical conditions, there has not been a single documented case of either a cutaneous or internal malignancy associated with this drug.[21] Modified Kligman regime is still used as first-line treatment for melasma by dermatologists all over the world. The various therapies along with their level and quality of evidence are given in tables 1 and 2.

Table 1: United States' preventive services task force levels of evidence for grading clinical trials

Quality of evidence	
I	High quality evidence obtained from at least one well-performed randomized controlled trial
II-i	Evidence obtained from well-performed randomized controlled trials without randomization
II-ii	Evidence obtained from well-performed cohort or case control analytic studies, preferably from more than one research group
II-iii	Low quality evidence obtained from multiple observational studies with or without the intervention
III	Opinions of respected authorities based on clinical experience, expertise and descriptive studies
IV	Evidence inadequate owing to problems of methodology (e.g., sample size, length, or comprehensiveness of follow-up or conflicts in evidence)
Level of evidence	
A	There is good evidence to support the use of the procedure
B	There is fair evidence to support the use of the procedure
C	There is poor evidence to support the use of the procedure
D	There is fair evidence to support the rejection of the use of the procedure
E	There is good evidence to support the rejection of the use of this procedure

Table 2: Level and quality of evidence for therapies in melasma

		Therapy	Level of evidence	Quality of evidence
Epidermal melasma	Topical	2% HQ[22]	II-ii	C
		4% HQ[4,23-25]	I	B
		4% HQ + 0.05% RA + 0.01% fluocinolone acetonide[10,14,21,26]	I	A
		20% Azelaic acid[22,23]	I	B
		0.05% RA[14]	I	C
		Adapalene[27]	II-ii	B
		Kojic acid[28,29]	II-i	B
		Vitamin C[30]	I	B

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Table 2: Level and quality of evidence for therapies in melasma

		Therapy	Level of evidence	Quality of evidence
	Chemical peels	10–50% GA[31]	II-ii/II-iii	C
		70% GA[32]	II-i	B
		Jessner's solution[32]	II-i	C
		20–30% salicylic acid[33,34]	II-iii/III	C
		Lactic acid[35]	II-iii	C
		1–5% RA[36]	III	C
	Derma-abrasion[37]		II-iii	E
	Broad-spectrum sun protection[38,39]		II-i/II-iii	B
Dermal melasma	Lasers	Pulsed CO_2 laser followed by Q-switched alexandrite laser[40]	IV	C
		Q-switched ruby laser[41]	II-iii	C
		Erbium:YAG laser	II-iii	D
		Fractional laser resurfacing[42,43]	II-iii	C
		Intense pulsed light[44,45]	II-iii	C
		Copper Bromide[46]	II-iii	C

GA, glycolic acid; HQ, hydroquinone; KA, kojic acid; KF, Kligman's formula; RA, retinoic acid; TCA, trichloroacetic acid.

CONCLUSION

Melasma is a relatively common form of hyperpigmentation. There is no cure and the condition tends to recur; therefore, precautions need to be taken. The standard therapy for melasma is HQ, either as monotherapy or, more often, in combination with other agents such as topical corticosteroids and tretinoin. Fixed triple combination or modified Kligman's regime is time tested and remains first-line treatment even though there are so many newer skin lightening agents and cosmeceuticals. Supervised use under the direction of a dermatologist is good for the patient.

Editor's Note

In spite of so many newer and promising agents for melasma, topical hydroquinone and modified Kligman's therapy remain the most efficacious therapy for melasma, if used judiciously. Of course, one needs to monitor side effects and look for erythema, darkening- or pepper-like appearance to stop therapy.

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CHAPTER 9

Nonhydroquinone Based Therapies for Melasma

Latika Arya

INTRODUCTION

Melasma is a chronic and recurring disorder of pigmentation causing significant psychosocial impairment. The treatment is challenging, prolonged, and requires a judicious approach especially in dark skinned patients. Hydroquinone (HQ) although quite efficacious may have significant side effects including skin irritation, contact dermatitis and exogenous ochronosis. Hence, there is a growing need for alternative natural, safe, and efficacious skin lightening agents. Recent studies show that several non-HQ agents may also play an important role in therapy for hyperpigmentation.[1] These agents selectively target hyperplastic melanocytes and inhibit key regulatory steps in melanogenesis. The various non-HQ skin lightening agents can be classified into three major groups based on their mechanism of action (Table 1).

1. Drugs acting before melanogenesis
2. Drugs acting during melanogenesis
   a. Tyrosinase inhibition
   b. Anti-inflammatory and antioxidant effects
3. Drugs acting after melanogenesis
   a. Inhibition of melanosome transfer
   b. Increased turnover of epidermis.

Non-HQ agents are reviewed here with a focus on those that have clinical trial findings, supporting their efficacy.

Table 1: Mechanism of action of non-hydroquinone skin lightening agents

Mechanism of action	Skin lightening agents
Drugs acting before melanogenesis	Sophoraflavanone G, undecylenoyl phenylalanine, piperlonguminine, aromatic-turmerone
Competitive tyrosinase inhibition	Azelaic acid, arbutin, deoxyarbutin, aloesin, kojic acid, flavonoids, gentisic acid, mequinol
Noncompetitive tyrosinase inhibition	Glabridin, hydroxystilbenes (resveratrol, genitol), N-acetyl glucosamine
Antioxidant	Vitamin C, vitamin E
Inhibition of melanosomal transfer	Niacinamide, soy (soybean trypsin inhibitors)
Acceleration of epidermal turnover and desquamation	Hydroxy acids, salicylic acid, linoleic acid, and retinoic acids

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NONHYDROQUINONE SKIN LIGHTENING AGENTS

Kojic Acid

Kojic acid (KA) is a naturally occurring fungal metabolite derived from certain species of *Aspergillus*, *Acetobacter,* and *Penicillium*. It reduces hyperpigmentation by tyrosinase inhibition by binding to copper. It is the most popular non-HQ agent employed for the treatment of melasma.[2]

Kojic acid is used at concentrations ranging from 1 to 4%. Although KA alone is less effective than HQ 2%, combination with glycolic acid (GA) 10% and HQ 2% augments efficacy.[3] Addition of KA may be beneficial in patients who do not respond to HQ, as seen in a 12 week, split-face, randomized study of 40 Chinese women with melasma, wherein 2% KA in a gel containing 10% GA and 2% HQ had a greater improvement as compared to the same combination without KA.[3] In another split-face study of 39 patients, 2% KA/5% GA and 2% HQ/5% GA had an equal efficacy in lightening of pigmentation including melasma.[4]

However, KA is a known sensitizer and has been shown to be mutagenic in cell culture studies.

Azelaic Acid

Azelaic acid is a naturally occurring dicarboxylic acid, obtained from *Pityrosporum* cultures, and associated with the hypomelanosis in tinea versicolor. It is a reversible inhibitor of tyrosinase activity and has an antiproliferative and cytotoxic effect on abnormal melanocytes.[5]

Azelaic acid 15–20% has been found to be of equivalent efficiency to HQ 4% in the treatment of melasma and postinflammatory hyperpigmentation.[4] Combinations with topical tretinoin 0.05% and GA 15–20% are synergistic.[4]

Azelaic acid has an excellent safety profile but may cause transient erythema, stinging, pruritus, scaling, and allergic sensitization on rare occasions.

According to the editor, this is a wonderful product to use if one is intolerant to fixed triple combination cream.

Arbutin

Arbutin is one of the most widely prescribed skin lightening and depigmenting agents worldwide. Arbutin is a naturally occurring D-glucopyranoside derivative of HQ found in bearberry leaves that converts to HQ *in vivo*. It competitively inhibits tyrosinase and 5,6-dihydroxyindole-2-carboxylic acid polymerase activities in a dose dependent manner in cultured melanocytes.[1] It also inhibits melanosome maturation and is less cytotoxic to melanocytes than HQ. Higher concentrations may be more efficacious, albeit with a risk of paradoxical hyperpigmentation. Studies show that arbutin is less effective than KA for hyperpigmentation. However, α-arbutin and deoxyarbutin, the synthetic derivate of arbutin, have a higher efficacy and stability in comparison to arbutin.[2,4] An *in vitro* comparative trial showed that HQ, arbutin, and deoxyarbutin had similar inhibitory effects on tyrosinase activity.[6] In a clinical study, topical treatment with deoxyarbutin for 12 weeks resulted in a significant reduction in overall skin lightness and improvement in solar lentigines in a population of light-skinned or dark-skinned individuals respectively.[6]

Soy

Soy contains active ingredients like isoflavones, vitamin E, and serine protease inhibitors-soybean trypsin inhibitor and Bowman-Birk protease inhibitor. The protease inhibitors inhibit proteinase activated receptor 2 (PAR2) activation, thereby inhibiting melanosome transfer.[2]

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Furthermore, they have been shown to reduce ultraviolet B (UVB)-induced pigmentation.[4] The inhibition of melanosome transfer is reversible, thus its safety profile is excellent.

Total soy extract was found to have a mean 12% reduction in dyspigmentation in 14 out of 16 Latin women after 3 months.[4] A double-blind, placebo-controlled, 12-week clinical study of soy-containing moisturizer with broad-spectrum sunscreen (SPF 30) in 68 patients demonstrated significant improvements in the fine lines, mottled hyperpigmentation, blotchiness, and skin clarity at week 12.[4]

Niacinamide

Niacinamide is the biologically active amide of vitamin B3 and is found in many root vegetables and yeasts. It inhibits the transfer of melanosomes to keratinocytes thereby reducing pigmentation.[1] In a randomized, split-face study of 18 Asian women with hyperpigmentation, 5% niacinamide applied for 4 weeks significantly decreased the hyperpigmentation as compared to vehicle.[4] In another randomized, split-face study comparing niacinamide 4% cream with 4% HQ cream in the treatment of melasma (n = 27), similar colorimetric improvement was seen in both the study groups at 8 weeks.[4]

Licorice Extract

It comes from the root of *Glycyrrhiza glabra*. Its main component is glabridin, a tyrosinase inhibitor that was shown to reduce UVB irradiation induced pigmentation and erythema in guinea pigs when applied for 3 weeks.[4] It also exerts anti-inflammatory effects by inhibiting superoxide anion and cyclooxygenase activity.[1] Liquirtin another component of licorice, induces skin lightening by dispersing melanin.[2]

A 20% liquiritin cream applied twice daily for 4 weeks yielded a reduction in pigmentation in a double-blind, controlled, split-face study of 20 women with melasma.[4]

Vitamin C

Vitamin C works by inhibiting tyrosinase activity through interacting with copper. It acts as a reducing agent at various oxidative steps of melanin formation, hence inhibiting melanogenesis. However, it is rapidly oxidized and is of limited stability. Hence, stable esterified derivatives have been developed like magnesium ascorbyl phosphate (MAP), ascorbyl 6-palmitate, and tetrahexyldecyl ascorbate.[1] In a study of 34 Asian patients of melasma or solar lentigines, using magnesium-L-ascorbyl-2-phosphate, 19 patients demonstrated significant lightening, as measured by colorimetry.[4] A study comparing 5% ascorbic acid and 4% HQ in 16 female patients with melasma found 62.5% and 93% improvement respectively. Side effects were present in 68.7% with HQ versus 6.2% with ascorbic acid. Thus, although HQ showed better response, vitamin C may play a role as it is devoid of any side effects, either alone or in combination therapy.[1]

Vitamin E (α-Tocopherol Acetate)

Vitamin E (α-tocopherol acetate) has been shown to cause depigmentation by interference with lipid peroxidation of melanocyte membranes, increase in intracellular glutathione content, and inhibition of tyrosinase.[1] It also has photo-protective effects. It is often formulated together with vitamin C for its lightening effect.

A clinical double-blinded study showed a significant improvement of melasma and pigmented contact dermatitis lesions using topical vitamins E and C with the combination showing better results compared to the single-vitamin treatment groups.[1] Topical α-tocopherol

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is mostly used at concentration of 5% or less. Side effects such as allergic or irritant reactions can be rarely seen.

Retinoids

Retinoids cause inhibition of tyrosinase and epidermal melanin dispersion. They also interfere with pigment transfer to keratinocytes and accelerate pigment loss by enhancing the epidermal cell turnover. They allow increased access to other pigment-lightening agents. The prescription retinoids used for direct improvement in skin pigmentation are tretinoin and tazarotene. Tretinoin applied in 38 patients with melasma over a 40 week period showed 68% improvement. However, side effects in the form of erythema and desquamation were seen in 88% patients.[7] Retinol is not as effective as tretinoin or tazarotene in pigment lightening but is less irritating.[2]

NEWER PRODUCTS

A number of synthetic and botanical compounds derived from natural sources are being investigated for their potential role in reducing melanin production and pigmentation. Although many of them are still in the experimental/research trial phase, a few salient ones which show possible benefits are mentioned here. They could potentially be used as treatment for melasma after their role is established by larger, well-designed clinical trials in future.

Aloesin

It is a low-molecular-weight glycoprotein obtained from *Aloe* tree. It competitively inhibits tyrosinase and also tyrosine hydroxylase and -3,4-dihydroxyphenylalanine (DOPA) oxidase.[6] Due to its hydrophilic nature, its penetration is limited; hence is commonly used in combination with arbutin or deoxyarbutin for a synergistic effect.

N-Acetylglucosamine (Chitin)

N-acetylglucosamine (NAG) is an amino monosaccharide that works by inhibiting the conversion of protyrosinase to tyrosinase.[4] In a 10 week, double-blind, vehicle-controlled study of 202 women, a moisturizer with 2% NAG and niacinamide demonstrated significant improvement in reducing areas of facial spots and the appearance of hyperpigmentation.[4]

Rucinol (4-N Butylresorcinol)

It is a phenolic derivative which inhibits both tyrosinase and tyrosinase-related protein. In a prospective, double-blind, randomized, vehicle-controlled, split-face comparative trial of 32 female patients with melasma, a statistically significant lightening was seen with rucinol serum 0.3% applied twice daily for 12 weeks, after a 12-week follow-up.[8] A recent formulation of rucinol, as 0.1% liposomal cream has an improved stability and enhanced penetration.[8]

Octadecenedioic Acid

It is a dicarboxylic acid with structural similarity to azelaic acid. Its skin whitening effects are mediated by the stimulation of peroxisome proliferator-activated receptors (PPARs), which are nuclear receptors modulating synthesis of tyrosinase mRNA. In a comparative study on

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21 Chinese volunteers, 1% octadecenedioic acid cream applied on forearm for 8 weeks with a further follow-up of 4 weeks showed lightening up to 11% and in 90% of individuals as compared to 2% arbutin applied on the other forearm.[8]

Bioflavonoids

These are benzopyrene derivatives which can be classified into flavones, flavanols, isoflavones, flavanones, and anthocyanidins. They exert a potent antioxidant and anti-inflammatory action and act as a substrate competitor for the tyrosinases. They inhibit pigment induced by DOPA oxidation as shown in an *in vitro* comparative study.[8] Hesperidin is a flavanone present in citrus fruits. Its structure is similar to that of HQ and has been shown to inhibit tyrosinase activity in melanoma B16 cells and human primary melanocytes and suppresses ultraviolet A induced damage of fibroblasts and oxidative damage of collagen.[9]

Coffeeberry Extract

It has antioxidant properties. Application of coffeeberry extract for 6 weeks improved hyperpigmentation in 40 patients with photo damage.[1]

Mulberry Extract

It is derived from the root bark of the plant *Morus alba* L and contains flavonoids including mulberroside F. It is found to have skin lightening effect due to inhibition of tyrosinase and superoxide scavenging activity. IC50 (concentration causing 50% inhibition of activity of tyrosinase) is very low (0.396%) as compared to 5.5% for HQ and 10.0% for KA.[1] In a randomized controlled trial on 50 patients of melasma, mulberry extract was compared with vehicle and was found to have significant improvement in melasma area and severity index (MASI) score, average mexameter measurements, and quality of life scores in treatment group.[10]

Tranexamic Acid: Trans-4-(Aminomethyl) Cyclohexanecarboxylic Acid

It is a lysine analog. It decreases α-melanocyte stimulating hormone by its antiplasmin activity, thus reducing melanin synthesis. In a study on 100 Korean women with melasma, tranexamic acid given intradermally (4 mg/mL) every week for 12 weeks caused significant decrease in MASI score ($p < 0.05$), and 76.5% subjects reported lightening of melasma with minimal side effects.[8] Tranexamic acid emulsion applied on 25 melasma patients for 5–18 weeks produced marked subjective improvement in 80% subjects within 8 weeks without any significant side effects.[8]

Orchid Extract

It has antioxidant activity and efficacy is similar to vitamin C in melasma and lentigines, as shown in a study comparing orchid extract to 3% vitamin C derivative in 48 female patients.[1]

Pycnogenol

It is obtained from the bark of French maritime pine *Pinus pinaster*. Its main constituents are procyanidins, polyphenolic monomers, phenolic, or cinnamic acids. It has antioxidant and anti-inflammatory properties. Oral pycnogenol has been found to reduce melasma severity although studies on topical use are lacking.[1]

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Boswellia (Boswellic Acids)

They are pentacyclic triterpenes extracted from the gum resins of the tropical tree *Boswellia serrata*. Boswellic acids are found to exert significant anti-inflammatory and pro-apoptotic activity as determined by several *in vitro* studies and clinical trials.[1]

Epigallocatechin-3-Gallate

It is obtained from green tea leaves and has been demonstrated to modulate melanin production in dose-dependent manner and also possesses anti-inflammatory properties.[8] However, more *in vivo* studies are needed to substantiate this action.

Ellagic Acid

It is isolated from green tea, eucalyptus, and strawberry and found to inhibit tyrosinase activity in B16 melanoma cells comparable to arbutin. In an open label randomized controlled trial on 30 patients of melasma, combination of plant derived and synthetic ellagic acid was compared with arbutin and significant improvement in pigment density was found on mexameter in all groups with no statistical difference between them.[10]

Hydroxystilbene Compounds

Resveratrol is one common example shown to reduce not only tyrosinase activity but also microphthalmia-associated transcription factor (MITF) expression in B16 mouse melanoma cells.[6]

Gentisic Acid

It is derived from gentian roots. Its alkyl ester, especially methyl gentisate, is a highly effective skin lightening agent and less cytotoxic than HQ.[8]

Silymarin

It is a naturally occurring polyphenol flavonoid compound derived from thistle plant *Silybum marianum*, which has tyrosinase inhibitory and antioxidant effects.[8] In a randomized controlled trial on 96 subjects, it showed significant improvements in macule size, MASI scores, and physician assessments compared to vehicle.[10]

Alpha Lipoic Acid/Thioctic Acid/Dihydrolipoic Acid

It is a disulfide derivative of octanoic acid. Its combination product with zinc-sodium zinc dihydrolipoylhistidinate has been studied by Tsuji Naito et al. on B16 melanoma cells and found to inhibit dopachrome formation.[11]

Dioic Acid

It belongs to the dicarboxylic acid group and acts as agonist to nuclear PPAR, which regulates tyrosinase transcription and melanosome transfer. In an open, comparative 12 week study on 96 Mexican female patients with melasma dioic acid was found to be an effective and highly tolerated skin product for melasma compared to 2% HQ.[8]

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Linoleic Acid

It is an unsaturated, 18 carbon fatty acid derived from hydroxylated botanical oils, e.g. safflower. It accelerates tyrosinase degradation and turnover of stratum corneum. Lincomycin is a lincosamide antibiotic produced by actinomycete, *Streptomyces lincolnensis* which inhibits melanogenesis post-transcriptionally. The efficacy of these drugs is proven in *in vitro* studies.[8]

Umbelliferone or 7-Hydroxycoumarin

It is a phenolic compound found in many plants from the Apiaceae (umbelliferae) family, such as carrot and coriander. Umbelliferone absorbs ultraviolet light and also has antioxidant and anti-inflammatory properties.[1]

Rumex Occidentalis

Rumex occidental is a perennial herb, native to California, has been reported to be a greater inhibitor of tyrosinase activity, as compared to arbutin, turmeric, and HQ in *in vitro* studies. In a randomized, double-blind, placebo-controlled trial in forty-five subjects with melasma, 3% Rumex occidentalis cream was found to be a safe and effective skin lightening agent with comparable efficacy to 4% HQ cream.[12]

Turmeric

Turmeric a traditional remedy used in India contains curcuminoids and volatile oils including turmerones which have been shown to have a suppressive activity on α-MSH-stimulated melanogenesis and may involve the down regulation of MITF and its downstream signal pathway.[13]

Emblica

It is an active ingredient derived from the fruit of *Phyllanthus emblica*. It has been seen to improve skin lightening by inhibiting tyrosinase and by its antioxidant activity. In addition, it increases collagen production and reduces matrix metalloproteinase-1.[14]

Belides

Belides is a new botanical ingredient obtained from *Bellis perennis* flowers which acts on nearly all the stages of the melanin synthesis process. It inhibits the proinflammatory mediator endothelin-1 and promotes the reduction of α-MSH receptor binding, with consequent reduction of eumelanin production. It also reduces the formation of free radicals and decreases the transfer of melanosomes to keratinocytes.[14]

In a study, a cream with belides, emblica, and licorice 7% applied twice a day, showed similar efficacy as hydroquinone 2% in the treatment of melasma, and with lesser adverse effects.[14]

Methimazole

It is an antithyroid agent found to inhibit melanin synthesis. Application of 5% methimazole cream once daily has been reported to successfully treat melasma resistant to hydroquinone, with advantages of high tolerability, non-mutagenicity, and non-cytotoxicity.[15]

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BOX 1 Newer combinations[16]

- Arbutin (deoxyarbutin) and aloesin
- Licorice extract, soy, and ascorbic acid (magnesium ascorbyl phosphate)
- Kojic acid, phytic acid, and butylmethoxydibenzoyl methane
- Azelaic acid 20% and tretinoin 0.05% or 0.1%
- Mequinol 2% and tretinoin 0.01%
- Hydroquinone 2%, kojic acid 2%, and glycolic acid 10%
- Mequinol 2% in combination with 0.01% tretinoin, tetrahexyldecyl ascorbate, glabridin (licorice extract), niacinamide, retinol
- 20% azelaic acid with mandelic acid, phytic acid, 4-n-butylresorcinol, and ferulic acid

Mequinol

Mequinol or 4-hydroxyanisole (4HA) is a tyrosinase inhibitor that is less irritating than hydroquinone and has no known cytotoxicity to human melanocytes. In a case series of 5 men with melasma, mequinol 2%/tretinoin 0.01% topical solution was found to be highly effective and well-tolerated. It is commercially available in Europe.[15]

Undecylenoyl Phenylalanine

It is a skin lightening agent which probably acts as α-MSH and β-adrenergic receptor antagonist. It has been shown to achieve a significant lightening of melasma lesions with minimal side effects.[15]

COMBINATION THERAPY

Combination of multiple ingredients in one formulation is preferred in order to synergistically produce pigment lightening by targeting various mechanisms of action mentioned earlier. This increases the efficacy compared to monotherapy and reduces the risk of adverse effects. Some combinations of skin lightening agents that have been studied in various trials are mentioned in Box 1.

CONCLUSION

Melasma has a very complex pathogenesis and further research is required to unravel its intricacies, and thereby develop newer therapies targeting this enigmatic disorder. Although prescription HQ products remain the gold standard, numerous non-hydroquinone, botanical, and other natural ingredients produce significant skin lightening, and newer agents are being discovered by the day. These agents target the key regulatory steps in melanin synthesis and are usually devoid of any significant side effects. Suitable combinations of these agents need to be designed and evaluated on a large-scale clinical trial to provide an appropriate therapeutic tool for this frustrating disorder.

Editor's Note

Of all non-hydroquinone therapies, only kojic acid, azelaic acid, deoxyarbutin, butylresorcinol, vitamin C, niacinamide, and dioic acid have some evidence in literature regarding their efficacy. More experience is needed with botanicals to substantiate their claims of effectiveness.

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CHAPTER 10

Oral Agents in the Treatment of Melasma

Maria Suzanne L Datuin-De Leon, Evangeline B Handog

INTRODUCTION

Melasma is a common acquired pigmentary disorder that mainly affects sun-exposed areas of the face, neck, and even the arms. It is the most common pigmentary disorder among Asians[1,2] that is difficult and challenging for both the dermatologist and the patients. It is more frequently seen in women and in dark-skinned races.[3]

The accurate etiopathogenesis is not known but it is believed to be due to the interplay of several factors namely exposure to ultraviolet radiation (UVR), hormonal imbalance, genetics, and a reaction to topical cosmetics and skin products.

TRADITIONAL TREATMENT OF MELASMA

First-line treatment options are topical compounds that interfere with the enzyme tyrosinase and melanin production, photoprotection, or camouflage. Chemical peels are second-line treatment options while lasers and light are often used in refractory cases.[4]

Globally available topical agents include hydroquinone, kojic acid, azelaic acid, licorice, and arbutin, to name only a few. Protective measures against UVR such as broad-spectrum sunscreen use, sun protective clothing, and sun avoidance are all essential in the successful management of melasma.[5] Cover up make up are also commonly employed by women to camouflage hyperpigmented patches.

ORAL AGENTS FOR MELASMA

Systemic agents are now being further explored as monotherapy or as adjuncts in the treatment of melasma. Previously, three systemic compounds were discussed namely tranexamic acid (TA), pycnogenol/procyanidin and *Polypodium leucotomos* (PL).[5] More recently, melatonin and carotenoids have been studied for their antimelanogenic effects.

Tranexamic Acid

Tranexamic acid has the most evidence among the oral agents used to treat melasma. TA has been used topically, as intralesional localized microinjections or systemically, but this chapter will focus on the effects of the latter route of administration. There are several proposed mechanisms for its antimelanogenic effects.

Tranexamic acid is a synthetic lysine analog that reversibly blocks lysine binding sites on plasminogen molecules. This effectively inhibits plasminogen activator (PA) from converting plasminogen to plasmin. Keratinocytes are known to produce PA and plasminogen molecules, which are found in epidermal basal cells.[5] TA blocks binding of plasminogen to keratinocytes, decreasing free arachidonic acid, and the subsequent production of prostaglandins, known to stimulate tyrosinase activity.[6]

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Plasmin also has a role in the release of basic fibroblast growth factor, which is a potent growth factor for melanocytes.[7] In animal models, TA has been shown to prevent ultraviolet light-induced pigmentation by preventing the binding of plasminogen to keratinocytes that resulted in a decrease in the tyrosinase activity of melanocytes.[8] Wu et al. reported that research by Zhang et al. showed that TA inhibited melanogenesis by interfering with the catalytic reaction of tyrosinase.[8] Other studies demonstrated that TA is also able to decrease α-melanocyte stimulating hormone (α-MSH) that stimulates melanin synthesis.[2]

More trials have recently been published on the efficacy of oral TA for melasma, either given as monotherapy or in combination with other treatment modalities like lasers or topical lightening creams. TA was given at doses ranging from 500 to 1,500 mg per day in two or three divided doses, but the most common dose is 250 mg twice daily.[3,5,9-12] Clinical trials ran for 2–6 months, with noticeable improvement seen as early as the first month of use.[8] Pooled data from a meta-analysis done by Kim et al. showed that TA is beneficial for melasma, with oral TA resulting in the greatest decrease in Melasma Area and Severity Index (MASI) scores compared to intralesional or topical TA.[13] Also notable was that while melasma lesions improved during treatment, non-melasma pigmented lesions such as lentigines and ephelides remained unchanged.[8] One study, however, reported that exogenous ochronosis in two subjects significantly improved with TA.[3]

Side effects of TA were few and characterized as mild or minor. These include nausea, belching, diarrhea, abdominal pain, oligomenorrhea, palpitations, skin rashes, alopecia, headache, drowsiness, and hyposexuality.[5,8,13] There have been no reports of thromboembolic events such as deep venous thrombosis, myocardial infarction, or pulmonary embolism from the intake of low dose TA.[13]

Pycnogenol/Procyanidin

Pycnogenol is a standardized extract of the bark of the French maritime pine, *Pinus pinaster*, and contains several phenolic compounds, chief of which is procyanidin (65–75%).[2] Pycnogenol's other phenolic compounds include catechin, epicatechin, caffeic acid, and ferulic acid.[14] It possesses anti-inflammatory and antioxidant properties, being more potent than vitamins C and E *in vitro*.[1,14,15] It has been demonstrated to protect against UV-induced erythema through mechanisms that inhibit the expression of nuclear factor (NF)-κB.[14] It has high bioavailability and low incidence of side effects.[2]

An open label trial evaluated pycnogenol at a dose of 25 mg thrice daily for 30 days. Results showed a reduction in pigment intensity ($p < 0.001$) and melasma area ($p < 0.001$) in 80% of the subjects. There were no side effects, with blood and urine test parameters within the normal range. In addition to its antimelasma effects, other symptoms such as fatigue, constipation, body pains, and anxiety also improved.[1]

A randomized, double blind, placebo-controlled trial, evaluated a fixed combination of 24 mg oral procyanidin plus vitamins A, C, and E twice daily in 60 Filipino females with epidermal melasma. The trial ran for 8 weeks and outcomes measures were the melanin index (MI) scores and MASI scores. Fifty-six subjects completed the study with a reduction in MASI scores in both placebo and treatment groups ($p = 0.001$) and a significant reduction between the two groups ($p < 0.0001$). The MI score was also significantly reduced in weeks 4 and 8 ($p < 0.0001$). No serious adverse events were reported.[15]

Polypodium leucotomos

Polypodium leucotomos is a tropical species of fern that possesses antioxidant and photoprotective properties. It is able to maintain the structural integrity of the extracellular matrix that is usually damaged by UV-induced expression of matrix metalloproteinases.[16]

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Two placebo-controlled trials evaluated oral PL in a total 61 females.[15-19] Both studies ran for 12 weeks; the dose was not stated in the first trial, but PL was given twice daily, while the second trial involved a daily dose of 720 mg of PL in three divided doses. Results were conflicting as the former study showed an improvement in 63% of subjects, with worsening observed in 17% of subjects in the placebo group.[16,17] Conversely, the second trial showed only 28% improvement in the PL group, but that PL was not statistically better than placebo.[19]

Melatonin

Melatonin is a hormone produced by the pineal gland and has been shown to have antioxidant and photoprotective properties.[18,20] It is able to reduce UV-induced cell death in cultured fibroblasts by being an effective membrane peroxidation inhibitor and by preventing cell cycle arrest.[20] It has been proposed that its antimelanogenic effects are due to its ability to decrease UV-induced free radicals as well as in inhibiting α-MSH.[18]

A double-blind study conducted by Hamadi et al. evaluated the efficacy of 3 mg oral melatonin and 5% melatonin cream for melasma. Thirty-six patients with epidermal melasma were randomized into four treatment groups: (i) melatonin cream, (ii) melatonin cream plus sunscreen, (iii) both oral and topical melatonin, and (iv) hydroquinone cream. All treatments were given for 90 days. The main outcome measure was the MASI score and secondary outcome measures were plasma malondialdehyde (MDA) and glutathione (GSH) levels as markers of oxidative stress. At the end of the 90-day period, MASI scores fell significantly across all treatment groups ($p < 0.05$). The group with both oral and topical melatonin showed superior results to the group that received topical melatonin only. There was decrease in MDA levels and increase in GSH levels in the first three groups which showed that melatonin's effects are in part due to its antioxidant properties. No adverse reactions were reported.[21]

Carotenoids

Carotenoids are micronutrients that have been demonstrated to possess antioxidant and free radical scavenging properties. In high concentration, there is preferential accumulation and bioactivity in the skin. Carotenoids protect against UV-induced skin damage and possess absorption spectra in both the UVA and UVB range. Aside from having antioxidant and anti-inflammatory properties, carotenoids have been reported to block the formation of melanin and to reduce the amount of existing melanin in melanocytes.[22]

A double blind, randomized, placebo-controlled trial compared an oral supplement containing colorless carotenoids, in addition to a topical lightening cream containing several tyrosinase inhibitors, antioxidants, and mild exfoliating acids for the treatment of melasma. Forty-four patients were randomized to receive either 800 mg of a proprietary brand of colorless carotenoids or placebo. Patients were evaluated at baseline, day 54 and day 84 using the modified MASI (mMASI), photographic documentation, as well as melanin and erythema indices using a mexameter. Only 36 patients completed the study but all 44 were included in the analysis. There was a significant reduction in the median mMASI score in both groups (both $p < 0.001$) but there was a greater decrease observed in the group that received the carotenoids (–2.1 vs. –1.8, $p < 0.379$). The MI also decreased in both groups but the intergroup difference was marginal. The erythema index showed significant improvements in both groups, with greater improvement in the treatment arm, compared to placebo.[22]

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CONCLUSION

While topical therapy and photoprotection are the mainstays in the treatment of melasma, the relatively slow response to treatment, prolonged application and limited efficacy are factors which cause patients to abandon treatment.[23] Oral agents may be used in cases of refractory melasma, either as primary or as adjunctive therapies, especially when compliance to topical therapy is difficult or has proven ineffective.

Among the oral agents, TA has the most evidence to date and has been shown to produce relatively fast results. It also has a good safety profile of up to 4.5 g a day for long-term use, much higher than the usual dose of 500–750 mg per day for melasma.[18] No serious side effects have been reported till date. More randomized controlled trials with larger sample sizes are needed in order to establish the safety and efficacy of other oral agents.

Editor's Note

Out of oral agents for melasma, tranexamic acid has a fairly good profile regarding safety and efficacy, although long-term observation of side effects is still warranted. Oral melatonin and carotenoids have exciting possibilities for treatment of recalcitrant melasma in future.

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CHAPTER 11

Chemical Peels for Melasma

Shehnaz Z Arsiwala

INTRODUCTION

Melasma is a chronic acquired hypermelanosis of persistent nature and resistant to therapies with a tendency to recur. No single therapeutic modality is sufficient to achieve total clearance of pigmentation in melasma and maintenance of response is a true challenge. Therefore, therapies need to be combined to optimize the outcome.

Current melasma therapies include:

- Topical therapies
- Oral therapies
- Interventional therapies.

A framework of sequencing therapies constitutes melasma treatment with topical therapies forming the mainstay of the treatment. The primary approach constitutes usage of topical therapies in single, dual, or triple combinations with or without hydroquinone (HQ) along with a broad spectrum sunscreen. The interventions, when sought have to be adjunctive to topical therapies. The practical considerations while executing interventions in melasma are highlighted in Box 1.

INTERVENTIONAL THERAPIES

The interventional and procedural based therapies in melasma:

- Chemical peels
- Lasers and lights

This chapter deals with practical and evidence-based considerations for chemical peeling in melasma.

CONCEPT OF PEELS IN MELASMA

Chemical peels achieve tissue replacement by destruction, elimination, and regeneration of epidermis and a part of dermis all through a controlled stage of inflammation. The peeling agent used can cause elimination of epidermal melanin, elimination of the melanin from

BOX 1 Practical considerations for interventions in melasma

- Never as first-line therapy
- Always adjuvant to topical therapies
- Introduced for unresponsive or recalcitrant cases
- Recurrences are common and multiple sequential treatments in combinations are required
- Optimum clearance and maintaining remission is difficult

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the keratinocytes, as well as melanosomes transfer to the keratinocytes, thus useful for the epidermal pigment component of melasma. While treating Indian skin types, the superficial peels are often used for safety and prevention of postinflammatory hyperpigmentation over medium depth to deep peels. The superficial peels are helpful but results may be variable and multiple sessions and rotational treatments may be required. Also, maintenance with topical therapy is mandatory. Medium depth and high strength peels are effective but risk of postinflammatory hyperpigmentation in skin of color, judicious use and excellent priming as well as post peel care are essential. Recurrence in melasma is very common and pigment improvement may be only partial thus limiting applications of peels in dark skin types.

Peels are never used as a primary choice but often used as second line and for recalcitrant melasma. While the chemical peels may work to a certain extent on epidermal pigment in melasma, the dermal pigment in melasma does not respond well to peels. Chemical peels can be combined with triple combination formula to hasten the efficacy, especially in mixed epidermal and dermal melasma.

Evidence from literature reflects that clearance of melasma is better and faster when chemical peels are combined with topical therapy. The peels studied are α-hydroxyl acid (AHA) peels like glycolic acid (GA), mandelic acid (MA), β-hydroxyl acid (BHA) peels, e.g., salicylic acid (SA) and combination peels like Jessener's and tretinoin peels. Box 2 highlights favorable features for peels in melasma.

Ground Rule for Peels in Melasma

Conducting peels in an Indian skin differs and cannot be followed along the lines of Fitzpatrick skin type I–III. Peels should be conducted on well informed, sun protected compliant patients with realistic expectations. For skin of color with melasma while conducting peels, excellent priming ensures adequate suppression of neomelanogenesis.

PEEL CONSIDERATIONS FOR MELASMA

- Choosing right patient
- Adequate priming
- Choosing right peel—formulation and technique.

Choosing the Right Patient

A sun protected patient who has completed at least 3–5 months of topical therapy should be considered for peels. A right candidate is one with predominant epidermal pigment. Thorough counseling regarding peeling as an adjunctive intervention and emphasis on adherence to topical therapy is crucial. A predominant epidermal pigment as reflected by Woods light examination would be a good candidate for peels. Boxes 2 and 3 highlight favorable features and contraindications for peels in melasma.

BOX 2 Favorable features for peels in melasma

- Melasma <1 year of duration (early melasma)
- Epidermal component more favorable than dermal component
- Heterogeneous pigment pattern more favorable than homogenous pigment pattern
- Focal melasma yields better results than extensive pan-facial pattern

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BOX 3 Contraindications for peels in melasma

- Dermal component prominent
- Prolonged duration of melasma
- Suspicion of ochronosis
- Unrealistic expectations
- Coexisting inflammatory dermatoses
- Poor priming
- Active bacterial/viral infections
- Keloidal tendency

Priming before Peels in Melasma[1,2]

Choosing a right and specific priming agent is essential. Hydroquinone is the gold standard for priming before peels. The depigmenting effects of the HQ treatment become evident after 5–7 weeks. Treatment should be continued for at least 3 months. Peels can be added after 6 weeks of HQ which should be stopped 2 weeks before peels and restarted a week after.

Retinoids as priming agents can be used alone or in combination with kojic acid (KA) or arbutin or GA. Tretinoin priming is most commonly used, at least 4 weeks before peel is introduced. Adapalene and tazarotene can also be used for priming. Adapalene has the advantage of less irritation than tazarotene and tretinoin.

Disadvantage of retinoids is stratum corneum thinning with resultant irritation with increased sun sensitivity in some patients. A good emollient should be added while priming with retinoids. Retinoids should be stopped for a week before peels. One must also ensure to defer a peel procedure when patients exhibit retinoid dermatitis and initiated only when the dryness and inflammation settle down.

Glycolic acid is the most widely used agent for priming. GA (6–12%) is a good priming agent for peels in melasma and can be combined with tretinoin or HQ. GA is started at least 6 weeks before peels and stopped a week before and reintroduced after 5–7 days of peels.

Combination of agents for priming is gaining ground due to synergism and increased efficacy. Box 4 highlights the combinations of priming agents used. Initial triple combination therapy of HQ, tretinoin, and steroid forms a comprehensive priming agent for all cases of melasma; however, the limitations of triple combination warrant for judicious use and patient needs to be switched to monotherapy and non-HQ based therapies between peels in interim phase. Priming has to be initiated for 2–4 weeks before peels, and one should stop retinoids 4–7 days before peels and resume 4–5 days after.

Kojic acid is more effective in combination with other agents and is used twice a day for 1–2 months. It is started 3 weeks before peels and stopped a week before and reintroduced after 5 days. It has high sensitizing potential. Kojic acid is useful in patients who cannot tolerate HQ.

Topical vitamin C preparations are widely used in priming phase topically and orally as they are great antioxidants and the reducing property of vitamin C preparations acts synregisitically to improve pigmentation and additionally also prevents postinflammatory hyperpigmentation in post-peel phase. Ascorbyl glucoside (10–15%) forms a good topical therapy in a liquid base. It is also synergistic with other priming agents and forms a peel booster.

Sun Protection

- Broad spectrum sunscreen with sun protection factor (SPF) of 15 or above and ultraviolet A (UVA) coverage should be started well in advance
- Sunscreens have a photosensitizing property in certain patients which can be unmasked before the peel is undertaken
- One must choose a newer photo stable sunscreen with a physical block if possible.

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BOX 4 Priming combinations

- Hydroquinone: 2–4%
- Hydroquinone: 2–4%+ glycolic acid: 6–12%
- Retinoic acid: 0.025–0.05%
- Retinoic acid: 0.025–0.05% + glycolic acid: 6–12%
- 20% azelaic acid
- 20% azelaic acid + 0.05% retinoic acid
- Vitamin C: 10–15%+ hydroquinone: 2–4% + kojic acid: 2–5%
- Triple combination with fluocinolone acetonide or mometasone for a short period of 12 weeks only

Peeling Agents for Melasma

Alpha-Hydroxy Acid Peels

Glycolic Acid Peels

Weekly sessions of 30–70% GA peel for a series of 4–6 sessions are most commonly conducted peels in melasma (Fig. 1). Peels are timed from 2–7 minutes of contact and terminated, with increasing percentage of GA in subsequent sessions. Neutralization with sodium bicarbonate solution or cold water is necessary. Gel peels can be used for sensitive skin. Liquid peels have better bioavailability. Free acid peels are preferred over gel peels. Various studies in skin of color highlight value of GA peels and emphasize the significance of increased efficacy when 30–40% GA peels are combined with topical therapies like modified Kligman's formula, topical 10% GA, topical vitamin C, azelaic acid, and adapalene.[3-7] Some studies reported superior results when GA peel concentration was as high as 50% with topical therapies.[8] Sequencing peels with a triple combination topically has been studied to show a better efficacy in moderate to severe melasma when measured by spectrometry.[7]

Lactic acid (LA) peels are also small molecular weight AHAs and proved beneficial when used as 92% strength at pH 3.5. Double coats of LA are applied for 10 minutes every 3 weeks for epidermal component in melasma and have been compared to Jessener's peel and found to be safe and efficacious.[9]

Mandelic acid at 30–50% applied weekly or biweekly is another agent used for peels in melasma. Advantage over other agents is its anti-inflammatory actions and less erythema and synergistic effect with other peels and lasers.[3]

Phytic acid peels is a GA based slow release peel in combination with mandelic and LA as adjuvants with phytic acid as an antioxidant and peel booster to be applied under occlusion and does not need termination. In melasma, it can be used twice in a month for 4–5 sessions.[3,10]

Tretinoin Peel

Tretinoin peels are useful in melasma wherein 5–10% tretinoin is applied as a slow release peel and helps to eliminate epidermal pigment, reduce photodamage, and improve texture (Fig. 2). It is beneficial as the patients are already primed with topical tretinoin alone or in triple combination therapy. In melasma, the slow release tretinoin peel helps to reduce the epidermal pigmentation in addition to reduction of photodamage, and improvement of texture. Tretinoin peels versus GA peels in the treatment of melasma in dark-skinned patients has been studied by Khunger et al., in Indian patients where 1–5% tretinoin peel at 1% strength is applied for 4 hours once in a week, for 12 weeks and found to be of equal efficacy.[11] Combinations in retinol peel formulations include nicotinamide, ascorbic acid, glycolic acid, and ferulic acid. The combination formulas are actually either with pigment lightners and antioxidants as adjuvants or synergistic alpha hydroxyl agents to improve

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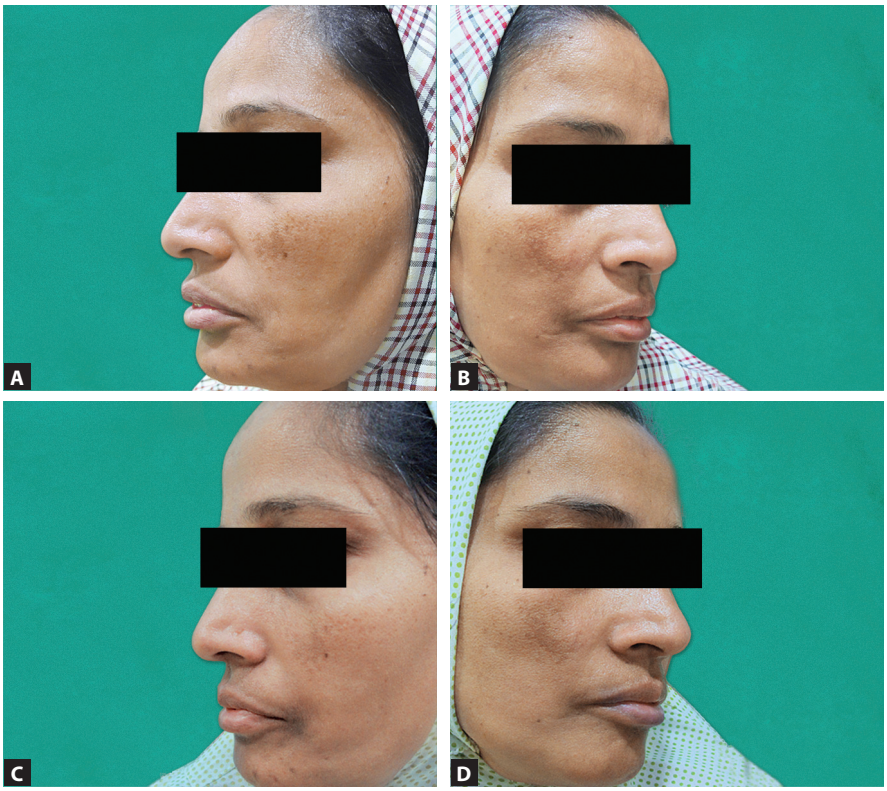

Figures 1A to D: **A** and **B,** Melasma before treatment; **C** and **D,** Melasma improvement after 6 sittings of 35% glycolic acid peels.

the peel outcome. A sequential combination peel is best avoided in a sensitive skin as exacerbation of post peel dryness and photosensitivity is high.

Salicylic Acid Peels

Salicylic peels in 20–30% strength help in elimination of epidermal pigment in well primed patients of melasma. Lipohydroxy acid peel has better keratolytic action and a smoother post peel texture but studies on superior efficacy over SA is lacking. Grimes study (1999) conducted five SA peels 20% and 30% pretreated with HQ 4% resulted in moderate to significant improvement in 4 out of 6 patients of dark skin with melasma. Hyperpigmentation was observed more in patients who were on non-HQ priming agents.[12,13]

Trichloroacetic Acid Peels

Trichloroacetic acid (TCA) peels work on principle of causticity. In lower strength of 15% TCA can be used as a superficial peel and at higher strength it can act as a medium depth peel. The TCA peel can be conducted at monthly interval for about four sessions and can be done 1–2 coats on melasma zone and single coat pan facially. It is a self-limiting peel and endpoint is frosting. Vigilance for postinflammatory hyperpigmentation is required even with low strength TCA peels in skin of color. Single coat of TCA peel creates a superficial peel. Increasing number of coats can make it medium depth. Frosting here acts as a guide to depth control.

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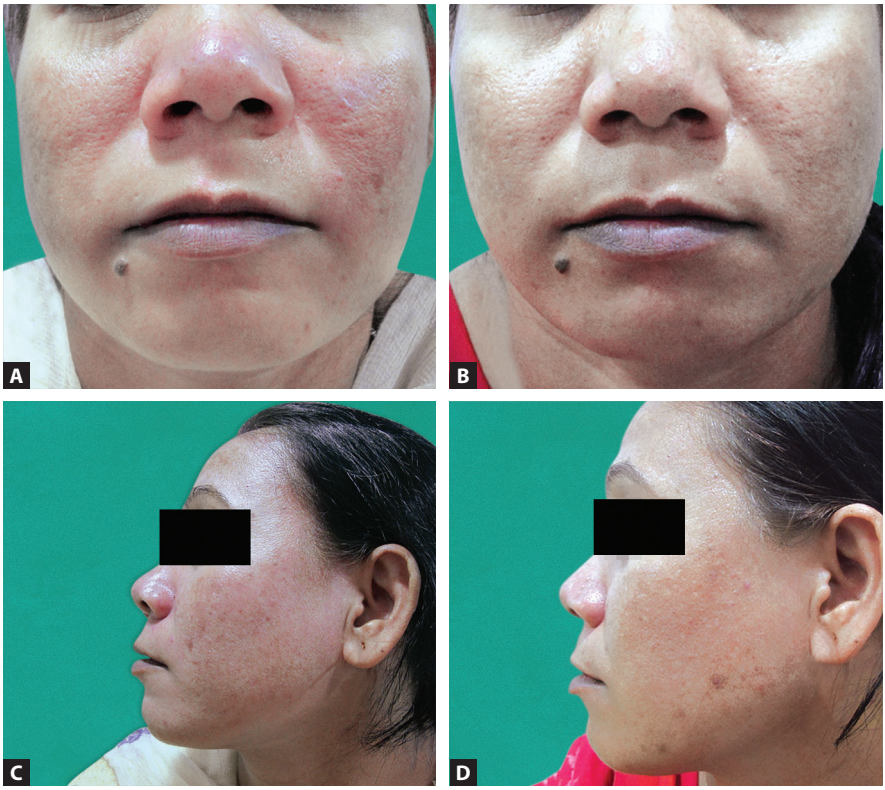

Figures 2A to D: A, Melasma before treatment; **B**, Melasma after yellow peels; **C**, Melasma before treatment; **D,** Melasma after yellow peels.

A comparative study of TCA versus GA chemical peels in the treatment of melasma reported that GA peel is associated with fewer side effects than TCA and has the added advantage of facial rejuvenation.[14] Kalla et al. reported degree of response was better with TCA but relapses were more common.[15] Topical ascorbic acid combined with 20% TCA peel in melasma improves the results and helps in maintaining the response to therapy[16] and better when TCA is used along with modified Jessener's peel.[17]

Newer combinations include azelaic acid, resorcinol, and phytic acid combination for improvement of melasma and as effective as 50% glycolic peels.[18,19]

Levels of evidence and strength of recommendations for various peeling agents in ethnic skin by US Task Force grades GA as A level and lactic acid, salicylic acid, TCA, and Jessener's peel as level B recommendation and level C recommendation for phytic acid and pyruvic acid peels in improvement of melasma. Evidence-based peels with levels of evidence are listed in Box 5.

When evaluating a case for peels in melasma, a physician must consider all the possible peel as well as nonpeel options available to improve the condition. Choose the ones with best results and minimal side effects. Consider the need to combine various techniques along with peels, e.g., microdermabrasion, lasers, etc.

Glycolic acid, TCA, Jessener's solution, SA, tretinoin, and KA peels are used. GA 20–50% is useful in dark skin types. Dermal melasma is unresponsive to chemical peeling treatment. Clearance of whatever degree requires maintenance with topical therapy. Post-peel care as listed in Box 6 needs to be followed rigorously in all cases.

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BOX 5 Evidence-based peels for melasma

- GA: 10–50% (LoE: C)
- GA: 70% (LoE: B)
- TCA: 10–25% (LoE: C)
- Jessener's peel: (SA + LA + resorcinol + ethanol) (LoE: C)
- SA: 20–30% (LoE: C)
- Retinoic acid peel: 1–5% (LoE: C)
- KA: 2–5% (LoE: C)
- Pyruvic acid: (50%) (LoE: C)
- Combinations
- GA (50%) + KA (10%) (LoE: C)
- Retinol peel: 5% (LoE: C)

LoE, level of evidence; GA, glycolic acid; TCA, trichloroacetic acid; SA, salicylic acid; LA, lactic acid; KA, kojic acid.

BOX 6 Post-peels care

- Post-peel care in melasma
- Ice compress
- Restrict emollients for 2 days
- Once peeling initiates start emollients if visible dryness
- Sunscreens are must
- Moisturizers may be required
- Advise mild gentle neutral pH facial cleansers
- Restart lightening agents at 1–2 weeks

Home peels for melasma include use of low strength peels like GA 20% or mandelic acid 18% at home by the patient on daily or biweekly basis to improve the pigment clearance, postulated theory is a regular intermittent low strength home peel in that excess keratin layers are removed by the peel thus permitting better penetration of hydroquinone.[20] According to the author, introduction of low strength home peels by the patient improves compliance and optimizes outcomes of in office based peels.

CONCLUSION

Though chemical peels are an adjuvant therapy in melasma and never used as a first-line therapy, they are a beneficial option for elimination or reduction of epidermal component of melanin and efficacy increases when peels are added to topical therapy. A large number of peeling agents are now emerging as evidence-based option for sequential treatment of melasma with topical therapy and sun protection. Choosing a right patient with adequate priming, adherence to sunprotection, and topical therapy with peels as interventions form a backbone to improve melasma in the current scenario.

Editor's Note

Chemical peels work well as adjuvants to topical therapies such as hydroquinone, modified Kligman's regime, azelaic acid, kojic acid, and others. They have more rejuvenating effects than lightening of pigmentation. They are useful modalities in the armamentarium of treatment of melasma but good priming is important for preventing post-peel hyperpigmentation. Conventional peels are more efficacious but combination and proprietary peels have fewer side effects.

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CHAPTER 12

Lasers for Melasma

Pooja Arora, Rashmi Sarkar, Neha Meena

INTRODUCTION

Melasma is a common, chronic acquired pigmentary disorder, which is recurrent and resistant to the treatment. Management of melasma includes use of topical agents like combination of hydroquinone, tretinoin and low potency steroid, glycolic acid, azelaic acid, kojic acid, arbutin, and vitamin C; chemical peels like mandelic acid, salicylic acid, and glycolic acid; as well as lasers and lights. In melasma, different types of lasers have been studied with variable results. In this chapter, various lasers used in melasma are discussed.

OVERVIEW OF LASERS IN MELASMA

Lasers, nowadays, play a pivotal role in the management of numerous dermatological conditions, especially in pigmentary disorders like melasma. Laser treatment of pigmented lesions is based on the theory of selective photothermolysis proposed by Anderson et al in 1983. It states that when a specific wavelength of energy is delivered in a period of time shorter than the thermal relaxation time of the target chromophore, the energy is restricted to the target and causes less damage to the surrounding tissue. Therefore, a laser should emit a wavelength that is specific for the chromophore being targeted and well absorbed by it.

Melanin has a broad absorption spectrum (wavelength between 630 and 1,100 nm). The longer wavelength (>600 nm) penetrates deeper in skin and required more energy for melanosomal damage. As the melanosomes have a short thermal relaxation time (250–1,000 ns), submicrosecond laser pulses are required for their selective destruction.

In 2004, Manstein et al introduced the fractional photothermolysis theory. Fractional lasers in melasma works by creating microthermal zones and photothermolysis leads to tissue destruction of melanocytes and melanin containing keratinocytes, which are further eliminated from the skin via melanin shuttle. This decreases the pigment content of both epidermal and dermal, thus resulting in improvement in melasma.[1]

VARIOUS LASERS IN MELASMA

The following types of lasers have been used in the management of melasma:

- Near-infrared: Q-switched neodymium:yttrium aluminum garnet (QS Nd:YAG (1,064 nm)]
- Red light: QS ruby (694 nm), QS alexandrite (755 nm)
- Green light: Flash lamp-pumped pulsed dye laser (PDL) (585 nm), frequency doubled QS Nd:YAG (532 nm).

Q-Switched Lasers

Q-switched lasers (QS Nd:YAG, QS ruby and QS alexandrite laser) works on the principal of selective photothermolysis of with nanosecond pulse duration for targeting the melanin. The preoperative procedure is mentioned in box 1.

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BOX 1 Preoperative preparation

- Fully informed written consent for the procedure
- Patient's counseling according to expected reasonable results
- History of allergy to topical anesthetics
- History of herpes labialis, if present, then prophylactic oral acyclovir or valacyclovir should be started 1 day prior to procedure and continued after procedure for 5 days
- Presence of keloid and/or hypertrophic scars
- History of topical/oral retinoid use
- Pretreatment photographs
- Pre- and posttreatment application of topical depigmenting agents, photoprotection, use of sunscreens
- Test spots (for Q-switched lasers)
- Eye protection, eye shields, universal precautions

Q-Switched Nd:YAG (1,064 nm)

Mechanism of Action

The QS Nd:YAG laser with its longer wavelength (1,064 nm), penetrates deep into the dermis and selectively absorbed by the melanin chromophore, thus leading to less damage of the epidermis and surrounding dermal tissue as it is not absorbed by hemoglobin. Low-dose QS Nd:YAG laser exposure results in the sublethal injury of the melanosomes by causing fragmentation and expulsion of melanin granules into the cytoplasm. Dermal vascular also play role in the pathogenesis of melasma. This factor is taken care of by the QS Nd:YAG (1,064 nm) laser by causing subcellular damage to the upper dermal vascular plexus. Thus, leading to the resolution of melasma.[2] Also, the injury to the surrounding dermal tissue by the subthreshold energy leads to cutaneous rejuvenation by neocollagen formation. This leads to brighter and younger looking skin (Figures 1 and 2).

Efficacy

The QS-Nd:YAG (1,064 nm) laser is the most commonly used laser in pigmentary disorders including melasma. The parameter used for the laser includes fluence less than 5 J/cm^2, spot size of 6 mm, and frequency of 10 Hz. The number of treatment sessions varies from 5 to 10 at 1 week intervals, depending upon the response to the treatment.

Studies on use of lasers in pigmentary disorders have reported variable results in both efficacy and side effect profile, including hypopigmentation and depigmentation after laser

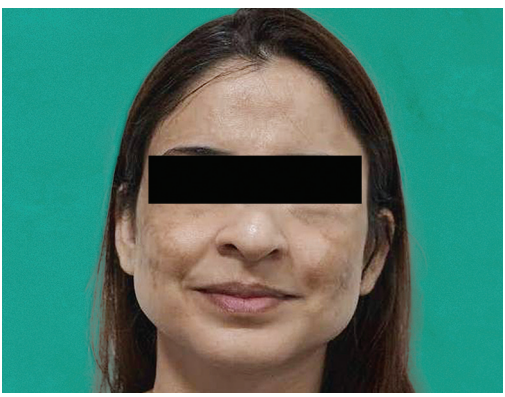

Figure 1: Centrofacial melasma at baseline.
Courtesy: Dr Latika Arya.

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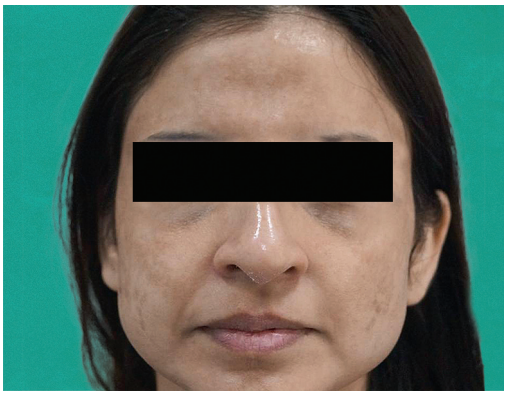

Figure 2: Good improvement in epidermal melasma (50–75%) on Physician Global Assessment scale after four sessions of low fluence Q-switched neodymium-doped yttrium aluminum garnet laser, performed every 10 days.
Courtesy: Dr Latika Arya.

sessions.[3,4] Laser-induced depigmentation may occur because of the direct phototoxicity and cellular destruction of melanocytes caused by the use of high fluence. Also, the subthreshold injury of the dermal tissue during repeated sessions, intrinsic uneven distribution of melanin pigmentation in the skin, and nonuniform laser energy output may further lead to depigmentation.[3] Follicular pigmentation loss may lead to whitening of fine hair. So, the number and frequency of laser sessions should be adjusted according to the clinical response and to be kept minimum (5–10) to prevent such post-laser therapy side effects. Laser therapy sessions should be stopped after earliest sign of hypopigmentation.

In contrast to the above findings, some studies have also reported rebound hyperpigmentation caused by the multiple subthreshold injuries that lead to the stimulation of melanogenesis in some areas. Other reported side effects include herpes simplex reactivation, physical urticaria, acneiform eruption, and petechiae.

Even after the initial good response to the laser therapy, there is a high recurrence rate of melasma. This warrants the repeated QS Nd:YAG laser sessions. Hence, lasers should be reserved only for refractory cases of melasma who have shown no or partial response to the treatment.

Q-Switched Ruby Laser (694 nm)

Mechanism of Action

Q-switched ruby laser (QSRL 694 nm) work on the principle of selective photothermolysis and causes highly selective destruction of melanosomes. However, due to its wavelength of 694 nm, QSRL is more selective for melanin compared to QS Nd:YAG laser (1,064 nm).

Efficacy

Studies have reported variable results in the efficacy of QSRL in the management of melasma. Tse et al. compared the efficacy and side effect profile of QSRL and QS Nd:YAG (1,064 nm) lasers in pigmentary disorders including melasma. They reported that QSRL showed better response compared to QS Nd:YAG laser.[5] However, QSRL treatment sessions were found to be more painful, while more postoperative discomfort was found in QS Nd:YAG laser. Further studies are required to support its role in the management of melasma. Zhou et al. used a high-density coverage fractional QSRL (694 nm) combined with levorotatory vitamin C

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in the treatment of melasma. They observed significant decrease in Melasma Area and Severity Index (MASI) score with fewer side effects.[6]

Erbium:Yttrium Aluminum Garnet Laser (2,940 nm)

Mechanism of Action

Water works as the chromophore for the erbium:yttrium aluminum garnet (Er:YAG) laser that emits light of 2,940 nm wavelength. Erbium:YAG laser causes skin ablation with minimal thermal damage and so, there is minimum risk of postinflammatory hyperpigmentation.

Efficacy

There is paucity of evidence on the efficacy and safety of use of Er:YAG laser in melasma. Er:YAG laser was used by Manaloto et al. to treat 10 female patients with refractory melasma with fluence levels of 5.1–7.6 J/cm. It showed remarkable improvement of melasma immediately after treatment.[7] Most common side effect noted in the study was the development of postinflammatory hyperpigmentation in 3 weeks to 6 weeks after the laser sessions in all the patients. This may be because of paradoxical stimulation of melanocytes in the treated area and inflammatory dermal reaction after the laser. However, the pigmentation resolved after use of depigmenting agents like azelaic acid, glycolic acid peel, and sunscreens. However, this side effect limits its use in melasma.

Pulsed Dye Laser (585 nm)

Mechanism of Action

Recent data suggests the role of cutaneous vasculature in the pathogenesis of melasma. Pulsed dye laser (585 nm) targets the melanin and cutaneous vasculature. Vascular endothelial growth factor receptors 1 and 2, expressed by melanocytes, are involved in the pigmentation process. Thus, by targeting the vascular component, the stimulation of melanocytes can be prevented. This results into better clinical response and decrease risk of recurrence of melasma.

Efficacy

There is paucity of studies of efficacy and safety profile of PDL in melasma. Passeron et al. studied 17 patients with melasma with PDL and triple combination cream (hydroquinone, 4%; tretinoin, 0.05%; and fluocinolone acetonide, 0.01%) in a split face study.[8] Three sessions were performed at 3 weekly intervals at the following settings: fluence 7–10 J/cm^2 and pulse duration 1.5 ms. They found that the combination treatment had a greater treatment satisfaction in patients with skin phototypes II and III. Postinflammatory hyperpigmentation was reported in 3 cases.

Fractional Lasers

Mechanism of Action

As mentioned earlier, the fractional laser works on the principle of fractional photothermolysis. There is formation of multiple microthermal treatment zones (MTZ) of thermal damage with leaving the surrounding skin intact. The damaged cells with melanin content (melanocytes and kerationocytes) are expelled out of skin as microscopic epidermal necrotic debris.[1] Studies have found variable results in melasma. Density of MTZs used in the melasma treatment varied from 2,000 to 2,500 MTZ/cm^2 and energy levels 10 to 15 mJ. Number of laser sessions varies from 2 to 6 at an interval of 1 to 4 weeks.

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Nonablative fractional laser therapy does not create an open wound. The stratum corneum is found to be intact after 24 hours of treatment. This results in faster recovery and fewer risk of scarring. Fractional lasers are good for the treatment of dermal melasma.

Efficacy

After the fractional laser sessions, Goldberg et al. have reported reduction in the number of melanocytes, thus leading to clinical resolution of pigmentary disorders.[9] In a randomized controlled trial by Kroon et al., 20 female patients with moderate to severe melasma were treated with either nonablative fractional laser (performed every 2 weeks for a total of four sessions) or triple combination topical cream (once daily for 8 weeks).[10] Laser sessions were done with density of 2,000–2,500 MTZ/cm^2 and 10 mJ energy per microbeam. Both group showed good results with more treatment satisfaction and recommendation was found in the laser group. Although, recurrence of melasma was seen in both groups, yet none of the cases develops postinflammatory hyperpigmentation.

Intense Pulse Light

Mechanism of Action

Intense pulse light (IPL) produces a noncoherent beam of light with the wavelength between 500 and 1,200 nm. It works by the absorption of light energy by melanin and lead to epidermal coagulation due to photothermolysis followed by microcrust formation.[11] These crusts containing melanin are shed off hence, the clinical improvement in pigmentation. For epidermal lesions, filters of 500–550 nm can be used and for dermal/mixed melasma cases, filters with higher wavelength are preferred. The fluence should be changed according to the site of treatment. Multiple pulses can be used as they reduce the thermal damage by allowing the epidermis to cool while the target stays warm.

Efficacy

Intense pulse light was used by Zoccali et al. in treatment of 38 patients with melasma, using cut off filters of 550 nm, pulse of 5–10 ms, pulse delay of 10–20 ms, and low fluence 6–14 J/cm^2 and found 80–100% clearance in 47% of patients after 3–5 sessions with no side effects.[12] The pulse duration used in the studies varied from 3 to 5 ms with an average pulse delay of 10–20 ms. Pulse delay of 10 ms or more is required as it prevent the thermal damage of the targeting tissue. Average number of sessions used in these studies were 2–5 at an interval of 4–8 weeks. However, more number of sessions is required for maintenance and it decreases the chances of recurrence.

Intense pulse light is found to be effective in the management of epidermal melasma, dermal, mixed, or refractory melasma. However, higher fluence are required in the refractory cases. In addition, the risk of postinflammatory hyperpigmentation should always be kept in mind. Prophylactic pre- and postprocedure sunscreens and depigmenting agents should be advised.

Combined therapy by both ablative and pigment selective lasers have also been used in melasma. Firstly, the ablative lasers remove the epidermis that contains melanin and abnormal melanocytes, followed by the use of pigment selective Q-switched lasers that penetrates deeper and targets dermal melanophages. This approach also reduced the postprocedural side effects.

LASERS IN THE FUTURE

Fodd and Drug Administration has approved fractional Er:YAG laser for melasma recently. Studies have shown marked response in melasma by thulium laser and copper bromide lasers.

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However, studies with larger sample size are required to confirm these results. Picosecond lasers are now available with laser output of 532, 755, and 1,064nm. Theoretically, these lasers may be more effective in removing pigment due to the shorter laser pulse duration that cause pigment fragmentation. The damage to surrounding tissue will also be much less. However, there is lack of studies of these lasers in melasma.

Laser assisted drug delivery is the use of lasers for the delivery of topical medications in dermal melasma where topical therapy has not shown good results. Ablative lasers like CO_2 and Er:YAG can be used to create trans epidermal channels and facilitate drug delivery to the deeper layers of the skin.

CONCLUSION

Lasers play a crucial role in the treatment of various dermatological disorders including melasma. Laser treatment offers the maximum efficacy with minimal side effects. The results depend upon the choice of laser and correct dose settings. Also, topical depigmenting creams and peeling agents remain the gold standard of therapy as they are evidence-based, cheaper, and of equal or greater efficacy compared to lasers. So, the use of laser should be restricted to refractory unresponsive melasma. Appropriate maintenance therapy and photoprotection should be used to avoid recurrence of melasma.

Editor's Note

Lasers at present, do not appear very promising and should be reserved for recalcitrant melasma where modalities such as topical therapies and chemical peels have failed. They thus form the third-line of therapy for melasma. Pulsed dye laser, thulium laser, and fractional lasers need to be tried cautiously for future. Laser toning is a procedure which may still give good results when tried in the hands of an experienced dermatologist. At best, lasers can be combined with fixed triple combination therapy for maintaining good results.

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CHAPTER 13

Melasma and Quality of Life

Shilpa Garg, Rashmi Sarkar, Amit G Pandya

INTRODUCTION

Quality of life (QOL) includes all the factors that have an impact on an individual's life. Health related quality of life (HRQOL) measures the physical, social, and psychological well-being of an individual and evaluates the burden of disease on daily life. Melasma negatively affects the HRQOL of an individual due to its location on the face and disfiguring skin discoloration that it causes. It has been shown to undermine the physical, emotional, psychological, and social functioning of an affected individual. It causes a multitude of psychological problems, including distress, and embarrassment, negative fear of evaluation, loneliness, social isolation, feelings of embarrassment, depression, and anxiety. Since Indian women are more prone to develop melasma due to their dark complexion and exposure to intense ultraviolet radiation, it is essential to measure the impact of melasma on their QOL and also the effect of any treatment on QOL.

ADVANTAGES OF MEASURING QUALITY OF LIFE

- Clinical: In guiding treatment decisions by evaluating the overall effect of skin disease on the patient and to monitor progress after treatment
- Research: To demonstrate that a treatment improves both clinical and psychological effects of a disease
- Audit: Quality of life is used as a criterion to judge the effectiveness of dermatology services based on patient satisfaction with disease management
- Political and Financial: Since most skin diseases are not life threatening, they are often below the funding cut-off point for granting agencies. In deciding resource allocation, QOL studies provide evidence of the overall burden of skin disease and impact on patients, helping to compare these diseases to non-dermatological diseases.

HEALTH RELATED QUALITY OF LIFE INSTRUMENTS AND QUALITY OF LIFE IN PATIENTS WITH MELASMA

Instruments to measure HRQOL are questionnaire based. There are general health questionnaires, dermatology-specific questionnaires, and disease-specific questionnaires. Dermatology-specific instruments measure the impact of skin disease on the patient's QOL whereas, disease-specific questionnaires measures the impact of diseases such as melasma on patients. The general health questionnaires are not widely used in dermatology.

- Dermatology-specific questionnaires: There are many dermatology-specific questionnaires. The two most commonly used HRQOL instruments are the dermatology life quality index (DLQI) and Skindex. Others include instrument proposed by Whitmore

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(21 questions assessing impact of skin disease on QOL), the American Medical Association (evaluating permanent skin impairment), Robinson (measuring disability in dermatology), the "leisure questionnaire" (evaluating impact of skin disorders on social activities), the impact of skin disease scale (IMPACT, evaluating the psychiatric morbidity in skin disorders), and the Bother Assessment in Skin Conditions Scale (BASC, evaluating how much patients are bothered by their skin condition using a horizontal visual analog scale)

- Dermatology Life Quality Index: The DLQI is a validated questionnaire that was developed by Finlay and Khan.[1] It contains 10 items which cover various aspects of an individual's life such as feelings, symptoms, daily activity, work, leisure, personal relationships, and treatment. The response of the patient is graded on a four-point scale ranging from "very much" to "not at all". The score of each item is added to give a total score ranging from "0" which represents "no effect" to "30" which represents "highest impairment to QOL." The questionnaire has been translated into various languages. Pichardo et al.[2] used the Mexican Spanish version of the DLQI and found that the mean DLQI score in 25 Latino poultry worker males affected by melasma was 7.5 as compared to 2.8 in men without melasma, the difference being statistically significant. In a study conducted on Singaporean women with melasma, it was found that the mean DLQI score was 4.5. This was lower than the DLQI score seen in patients with vitiligo (5.6), lichen planus (5.8), bullous pemphigoid (6.0), acne scarring (6.5), and pityriasis rosea (6.6). The higher DLQI score in other diseases compared to melasma could be because they are associated with more severe physical symptoms like pruritus and tenderness, which can adversely affect DLQI whereas, melasma causes minimum physical discomfort with greater psychological distress.[3] The mean DLQI score in an Indian study with 175 women with melasma was 1.46 with 73.71% patients not having any significant impact in their day-to-day life, 23.42 patients having mild effect and 2.85% having moderate effect in their day to day life. The lower DLQI score in this study could be due to the predominance of malar melasma in this study, freshly diagnosed cases with majority being less than one year and lower socio-economic status of the patients.[4]
- Skindex: This questionnaire was formulated by Chren et al.[5] It is a self-administered instrument which has 61 items consisting of two physical and three major psychosocial dimensions. The items include fear, anger, depression, embarrassment, social effects, physical discomfort, and physical limitations. Each of these items is graded on the scale ranging from 0 (no effect) to 4 (maximum effect). This instrument falls short in assessing the emotional well-being of the patient and focuses primarily on evaluating the impairment and disability in the physical functioning of an individual.
- Skindex-16: Skindex was condensed to Skindex-29 which was further modified to a brief; single-page Skindex-16 (Table 1).[6] It has superior ability to distinguish between patients with different QOL effects and focuses on how much patients are bothered by the diseases rather than the frequency of diseases. Hence, it is a better tool to assess the patient's handicap from a disease. Balkrishnan et al.[7] in their pilot study of 50 women found that the mean Skindex-16 in women with melasma was 55.8, which reflects the significant impact that melasma has on HRQOL. They also found that psychosocial factors were the predominant contributors to the increased HRQOL burden of melasma.

- Disease-specific HRQOL instruments: Disease-specific questionnaires are more accurate in the assessment of patient with a particular skin disease. All dermatology specific questionnaires measure the impact that various skin diseases have on QOL, including

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Table 1: Items of Skindex-16

During the past week, how often have you been bothered by:		
S. No.	**Items**	**Scale**
1.	Your skin condition itching	sx
2.	Your skin condition burning or stinging	sx
3.	Your skin condition hurting	sx
4.	Your skin condition being irritated	sx
5.	The persistence/reoccurrence of your skin condition	em
6.	Worry about your skin condition (for example, that it will spread, get worse, scar, be unpredictable, etc.)	em
7.	The appearance of your skin condition	em
8.	Frustration about your skin condition	em
9.	Embarrassment about your skin condition	em
10.	Being annoyed about your skin condition	em
11.	Feeling depressed about your skin condition	em
12.	The effects of your skin condition on your interactions with others (For example, interactions with family, friends, and close relationships, etc.)	fn
13.	The effects of your skin condition on your desire to be with people	fn
14.	Your skin condition making it hard to show affection	fn
15.	The effects of your skin condition on your daily activities	fn
16.	Your skin condition making it hard to work or do what you enjoy	fn

sx, symptoms; em, emotion; fn, functioning.

Note: Response choices for all items are a continuous bipolar scale with seven boxes anchored by the words "Never Bothered" and "Always Bothered" at the ends.

melasma. However, they lack the sensitivity for measuring the effect that pigmentary disorders have on QOL. The DLQI and Skindex measure the burden of the disease by giving equal weight to physical and psychological distress caused by skin diseases. To assess melasma with generic questionnaires like DLQI and Skindex presented a challenge as melasma causes negligible physical discomfort and a far severe psychosocial distress from dyspigmentation. Hence, a specific scale was required to measure HRQOL in patients with melasma and Melasma Quality of Life Scale (MELASQOL) was developed from questions more relevant to melasma-specific HRQOL issues and placed greater emphasis on the emotional and psychosocial aspects. It has shown high internal consistency, validity, and good discriminatory power compared to DLQI and Skindex-16

- Melasma Quality of Life Scale (MELASQOL): This instrument which was devised by Balkrishnan et al.[7] specifically emphasizes the HRQOL issues which are specific to melasma. It evaluates 10 items which primarily focus on the emotional and psychosocial aspects of melasma and ignores the physical symptoms. In the questionnaire, seven items are taken from the Skindex-16 and three items are taken from a skin discoloration questionnaire. The 10 chosen items showed highest correlation with both the Skindex-16 and skin discoloration questionnaire. Each of the items is scored using a Likert scale ranging between 1 (not bothered at all) and 7 (bothered all the time). The MELASQOL score ranges from 7 to 70, with a higher score indicating worse QOL. The various domains of the scale are shown in Table 2.

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Table 2: Melasma Quality of Life Scale (MELASQOL)	
1.	The appearance of your skin condition
2.	Frustration about your skin condition
3.	Embarrassment about your skin condition
4.	Feeling depressed about your skin condition
5.	The effects of your skin condition on your interaction with other people (eg. interaction with family, friends, close relationship etc)
6.	The effects of your condition on your desire to be with people
7.	Your skin condition making it hard to show affection
8.	Skin discoloration making you feel unattractive to others
9.	Skin discoloration making you feel less vital or productive
10.	Skin discoloration affecting your sense of freedom
Each of these 10 points is graded by the patient on a Likert scale of 1 (not bothered at all) to 7 (bothered all the time).	

This instrument which was first compiled in English language has now been translated and validated in various languages, including Spanish, French, Brazilian Portuguese, Persian, and Turkish, and Hindi.

The studies on MELASQOL conducted across various regions in different languages (Table 3) reveal that melasma has significant impact on the QOL as depicted by high mean MELASQOL scores.[3,7-16] Melasma seems to affect various domains of QOL like social life, recreation and leisure, emotional well-being, money matters, physical health, and family relationships. Hindi adaptation of the original MELASQOL (Hi-MELASQOL) was prepared and administered to 100 Indian women with melasma. The Hi-MELASQOL score was 18.15 $\pm$ 37,[17] with physical health, emotional well-being, and social life as most adversely affected life domains.[8]

In a study in which Brazilian MELASQOL was used to assess QOL in 51 women, 94.11% of women were bothered by the appearance of their skin, 64.71% felt frustrated and embarrassed, 52.94% were depressed, and 78.43% felt unattractive. However, 68.63% women felt that melasma did not affect their relationships with others, and 70.59% felt that it had no impact on the desire to contact or communicate with people, or spend time with others. Also, 86.27% had no difficulty in showing affection, 66.67% did not feel any reduced sense of importance or productivity, and 74.51% felt no restricted sense of freedom.[14] Another study from Brazil using MELASQOL to assess 56 patients observed that melasma on face caused great dissatisfaction, withdrawal from social life, low self-esteem and lower productivity at work and at school.[18] In an Indian study, using MELASQOL, melasma was found to have highly significant effect on the QOL with patients reporting feeling of frustration, embarrassment, and depression due to melasma. Forty percent of those affected bothered about melasma most of the times and 35% bothered all the time.[16] The severity of melasma assessed clinically by Melasma Area Severity Index (MASI) score does not correlate with the QOL of the affected patients in most of the studies suggesting that the clinical severity of the disease is not the only criteria by which the patients assess the burden of their skin condition.[3,7,9,10,18] This indicates that the therapeutic decisions cannot be solely based on the clinical findings and must incorporate the psychological impact of the disease on the patient. This also emphasizes the need for a melasma-specific questionnaire like MELASQOL in order to assess the psychosocial aspects of melasma. Patients with lower

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Table 3: Melasma quality of life scale in different languages

Authors	Language of MELASQOL	Mean MELASQOL score	Domains of MELASQOL most affected by melasma	Correlation between the QOL and disease severity
Sarkar et al.[8]	Hindi	37.19	Physical health, social life and emotional well-being	The Spearman's correlation between MASI and Hi-MELASQOL was 0.809 which implies that they are highly and positively correlated
Balkrishnan et al.[7]	English	36	Social life, recreation and leisure, emotional well-being	Moderate correlation between the QOL and disease severity (MASI)
Freitag et al.[9]	Brazilian Portuguese version	37.5	Emotional well-being	No correlation between the QOL and MASI score
Dominguez et al.[10]	Spanish	42	Social life, emotional well-being, physical health, money matters	Moderate correlation between the QOL and MASI score. (MASI score-10 and MELASQOL score-42)
Misery et al.[11]	French	20.9	Family relationships, social life	–
Dogramaci et al.[12]	Turkish	29.9	Appearance of the skin, frustration, feeling unattractive to others, having a restricted sense of freedom	Statistically significant correlation between the QOL and MASI score
Aghaei et al.[13]	Persian	52.83	social life, recreation and leisure, emotional well-being	Statistically significant correlation between the QOL and MASI score
Harumi and Goh[3]	English	25.6	–	No correlation between MASI with MELASQOL scores
Ikino et al.[14]	Brazilian version	34.4	Emotional well-being	–
Puri et al.[15]	Brazilian version	27.2	Emotional well-being, skin appearance, frustration, and embarrassment	–
Yalamanchili et al.[16]	English	28.28	Embarrassment and frustration	No correlation between MASI with MELASQOL scores

MELASQOL, melasma quality of life scale; QOL, quality of life; MASI, melasma area severity index.

educational levels and psychiatric disorders like mild depression and anxiety suffer higher emotional impact.

In a study of 300 patients (both men and women) of melasma from Brazil assessing Brazilian MELASQOL, 65% of patients reported discomfort due to melasma, 55% felt frustrated and 57% felt embarrassed. The study showed a significant improvement in the MELASQOL score from 44.4 to 24.3 after treatment with triple combination cream containing hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%.[19] In another study, participants reported improvement in HRQOL after treatment with the same cream.[17] Hence, HRQOL appears to be a useful tool to monitor response to therapy.

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CONCLUSION

As treating physicians, we must not only evaluate, treat, and monitor the physical findings of melasma, but also determine the impact that melasma has on the HRQOL of an individual. This aspect of the disease is also important in choosing therapy, as HRQOL can help guide treatment decisions, compare effectiveness of various treatment options, and monitor the disease after treatment is completed.

Editor's Note

The impact of melasma on HRQOL and the effect of treatment on MELASQOL scale would tell us how effective a treatment is for melasma in the future.

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CHAPTER 14

Melasma in Men

Rashmi Sarkar, Shilpa Garg

INTRODUCTION

Melasma is an acquired characteristic pattern of light-to-dark brown facial hyperpigmentation involving the sun-exposed areas. It is more commonly seen in women of childbearing age and in dark-skinned individuals of Hispanic, Asian, and African origin. However, melasma can occasionally be seen in men also and can be a source of distress and embarrassment with a negative impact on the quality of life due to its unsightly appearance and social stigma of being categorized as a disease of pregnant women.

EPIDEMIOLOGY OF MELASMA IN MEN

The exact prevalence of melasma is not known as being a cosmetic problem, many patients with choose to use over-the-counter products rather than consult with a dermatologist. Melasma is more commonly seen in women compared to men with overall prevalence in women varying between 1.5 and 33.3% by geography and population.[1]

However, barring few studies, there is a paucity of studies on melasma in men (Table 1). In a study by Vazquez et al.[2] from Puerto Rico, South America, men constituted only 10% of the cases of melasma. In contrast to this low incidence of melasma in Caucasian men, melasma is more commonly reported in men of Indian and Hispanic origin. In a study conducted by Pichardo et al.[1] on Latino men with melasma, data was pooled from three population studies. The prevalence of melasma reported from these three studies which included 25 poultry workers, cross-sectional study of 55 farm workers, and longitudinal study of 300 farm workers were 36.0%, 7.4%, and 14.0%, respectively. The prevalence of melasma across all the three studies was found to be 14.5%, which was higher than the prevalence of melasma reported in a random sample of Latino women (8.8%). In a simple survey in the dermatology clinic in Southeast Asia, melasma was prevalent in 40% women and 20% men.[3]

An Indian study by Sarkar et al.[4] in the year 2003 screened 120 patients of melasma and found that 31 (25.83%) of them were men. Out of these 31 male patients, 18 (58.06%)

Table 1: Prevalence of melasma in men

Author	Region	Prevalence of melasma in men (%)
Vazquez et al.[2]	Peurto Rico	10
Pichardo et al.[1]	Latino men	14.5
Sivayathorn et al.[3]	Southeast Asia	20
Sarkar et al.[4]	India	25.83
Sarkar et al.[5]	India	20.5

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were outdoor workers with 33.33% being policemen, 33.33% security guards, 11.11% construction engineers, and 22.22% laborers who worked at construction sites. In another study by Sarkar et al.,[5] 41 (20.5%) men with Fitzpatrick skin type III–V were identified as having melasma amongst 200 patients who were screened. Twenty-four (58.5%) men were outdoor workers and 12 (29.3%) men originally belonged to hilly regions of North India. This greater prevalence of melasma in Indian men compared to Caucasians could be due to their darker complexion compared to Caucasians, greater sun exposure due to their outdoor occupation, Indian climate with its hot, long, and dry summers and shorter winters, and increased cosmetic awareness amongst men.

ETIOLOGY

The exact cause of melasma is yet not clearly identified. However, multiple factors have been implicated in its pathogenesis including exposure to ultraviolet light, genetic factors, hormonal replacement therapy, oral contraceptives, thyroid dysfunction, cosmetics, phototoxicity, and antiepileptic agents. Out of these, the major etiological factors implicated in causing melasma include genetic influences, chronic sun exposure, and female sex hormones. The etiological factors causing melasma in men are likely the same as those implicated in women except for the hormonal factors (pregnancy, oral contraceptive pills, hormonal therapy, and mild ovarian dysfunction) which are considered as one of the most important etiological factors in causing melasma in women and probably do not hold a causative significance in men (Table 2). This may also explain the relatively low incidence of melasma in men compared to women. Besides the hormonal factors, other factors which are common between both men and women in causing melasma are sunlight, genetic factors, cosmetics, thyroid dysfunction, phototoxic, and antiseizure medications. Certain chronic diseases like nutritional and hepatic disorders and parasitic infestation have been implicated, although there is no clear evidence in their support.

In most of the studies[2,4,5] on melasma in men (Table 3), exposure to sunlight and family history were identified as the most common etiological factors for causing melasma and there was a statistically significant difference between men and women (Table 2). In women pregnancy (45.3%), sunlight (23.9%) and oral contraceptives (19.4%) were the major aggravating factors (Table 2).

Sunlight was reported as the most common aggravating factor in 45.16% and 48.8% men with melasma in the studies by Sarkar et al.[4,5] Sun exposure was found to be statistically significant higher in Indian men 20/41 (48.8%) compared to Indian women 38/159 (23.9%) with melasma (Table 3).[5] Similar findings were reported by Vazquez et al.[2] who studied 25 Puerto Rican and two South American men with melasma and found history of chronic sun exposure in 81.4% and worsening of melasma with exposure to sunlight in 66.6% patients. Another small study of two White and three Hispanic men with melasma also supported the role of chronic sun exposure.[6] In the study by Jang et al, based on histopathological findings, chronic ultraviolet radiation associated with signaling of paracrine cytokines was the main factor in the development of male melasma.[7]

Genetic predisposition also plays an important role in causing melasma in men. Sarkar et al.[5] reported a statistically significant higher frequency of family history in Indian men with melasma (39%) compared to women (20.1%). A positive family history was the most common aggravating factor (70.4%) in the study by Vazquez et al.[2] In this study, presence of melasma in close family members like mother, sibling, aunts, and uncle was reported in at least one family member, however, in none of the patients, father was affected by melasma. In a study by Keeling et al.,[6] involving series of five men with melasma, family history of

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Table 2: Etiological factors and clinical features of melasma in men and women[5]

Characteristics		Men (n = 41)	Women (n = 159)	p value
Aggravating factors	Sunlight	20 (48.8%)	38 (23.9%)	<0.05*
	Use of mustard oil	18 (43.9%)	50 (31.4%)	>0.05*
	Family history	16 (39.0%)	32 (20.1%)	<0.05*
	Chronic illness (post-typhoid period, thyroid disorder, inflammatory bowel disease)	5 (22.2%)	32 (20.1%)	>0.05*
	Phenytoin	3 (7.3%)	2 (1.3%)	NA
	Pregnancy	0	72 (45.3%)	NA
	Oral contraceptives	0	31 (19.4%)	NA
Age	Mean age (years)	33.5	31.5	>0.05†
	Range of age (years)	19–53	20–45	NA
Duration of melasma (years)	–	0.1–8.0	0.6–7.0	NA
Mean duration of melasma (years)	–	3.5	3.1	>0.05†
Clinical pattern of melasma	Centrofacial	12 (29.3%)	81 (51.0%)	<0.001‡
	Malar	25 (61%)	39 (24.5%)	<0.001‡
	Mandibular	4 (9.7%)	39 (24.5%)	<0.001‡
Wood light examination	Epidermal	28 (68.3%)	90 (56.6%)	0.85‡
	Mixed	9 (22.0%)	44 (27.7%)	0.85‡
	Dermal	4 (9.7%)	25 (15.7%)	0.85‡
Histopathological examination	Epidermal	10/20 (50%)	25/40 (62.5%)	–
	Mixed	9/20 (45%)	12/40 (30%)	–
	Dermal	1/20 (5%)	3/40 (7.5%)	–

NA, not applicable for significant testing.

*Z-test for testing difference between two different sample proportions

†Independent sample t-test

‡χ^2-test of significance; <0.001 highly significant; <0.05 significant.

melasma was present in all the patients in a first- or second-degree female relative, while two patients gave history of an affected male relative.

Among the cosmetics used by men, Sarkar et al.[5] reported the application of mustard oil in 43.9% of men with melasma which was in concordance with their earlier study.[4] Mustard oil is derived from the seeds of the mustard plant, which belongs to the family *Brassicaceae*. In certain states of India, this oil is used for cooking, body and hair massage, especially by men.[4] Mustard oil is a common photosensitizer in the Indian setup and can lead to facial pigmentation. However, more studies are needed to substantiate the role of mustard oil in causing melasma. In the study by Vazquez et al.,[2] use of various cosmetics like soaps, shaving creams, perfumes, and aftershave were identified in 25 (92.6%) men with melasma, although none of the patients attributed the development of melasma with the use of cosmetics.

Among the drugs (Table 3), only phenytoin was found as a causative agent in 6.45 and 7.3% men with melasma in the studies by Sarkar et al.[4,5] Only 1.3% women reported phenytoin as an aggravating factor (Table 2). Male patients treated with diethylstilboestrol

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Table 3: Characteristics of melasma in men

Author		Sarkar et al.[4]	Sarkar et al.[5]	Vazquez et al.[2]	Sialy et al.[8]
Total number of patients		Men (n = 31)	Men (n = 41)	Men (n = 27)	Men (n = 15)
Aggravating factors	Sunlight	14 (45.16%)	20 (48.8%)	18 (66.6%)	–
	Family history	5 (16.13%)	16 (39.0%)	19 (70.4%)	–
	Drug (phenytoin)	2 (6.45%)	3 (7.3%)	0	–
	Mustard oil application		18 (43.9%)	0	–
	Cosmetics (soaps, shaving creams, aftershave, perfumes)	–	–	25 (92.6%)	–
	Chronic illness (post-typhoid period, thyroid disorder, inflammatory bowel disease)	5 (22.2%)	–	–	–
Age	Range of age (years)	19–43	19–53	25–72	20–40
	Mean (years)	34.5	33.5	38.8	
Duration of melasma		2 months–4 years	1 month–8 years		2 months–1.5 years
Mean duration of melasma (years)		1.4	3.5	8	–
Clinical pattern of melasma	Centrofacial	15 (48.39%)	12 (29.3%)	12 (44.1%)	12 (80%)
	Malar	16 (51.61%)	25 (61%)	12 (44.1%)	2 (13.3%)
	Mandibular	0	4 (9.7%)	3 (11.1%)	1 (6.7%)
Wood light examination	Epidermal	15 (48.39%)	28 (68.3%)	18 (66.6%)	–
	Mixed	6 (19.35%)	9 (22.0%)	2 (7.4%)	–
	Dermal	10 (32.26%)	4 (9.7%)	7 (25.9%)	–
Histopathological examination	Epidermal	–	10/20 (50%)	4/5 (80%)	–
	Mixed	–	9/20 (45%)	1/5 (20%)	–
	Dermal	–	1/20 (5%)	0	–

therapy for prostate cancer developed melasma as a side effect.[8] Exposure to diethylstilboestrol and estradiol caused up to 20-fold upregulation of the enzyme tyrosinase-related-protein 2, which is involved in melanogenesis.[9]

Chronic illness were identified by 5 (22.2%) men (3 men had thyroid disorder, 1 had inflammatory bowel disease and 1 in post-typhoid period) and 32 (20.1%) women with melasma (Table 2).

Laboratory investigations in the study by Sarkar et al.[5] revealed anemia in 5 (12.2%) men, giardiasis in 2 (4.9%) men, and increased luteinizing hormone (LH) and low testosterone in 4 (9.7%) men. Similar hormonal profile was reported in another Indian study[8] which compared 15 male patients of melasma with 11 age matched controls. In this study, it was found that the mean circulating LH in men with melasma (6.42 ± 0.53 U/L) was significantly higher

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compared to controls (4.46 ± 0.57 U/L) ($p < 0.05$). There was no significant difference in the levels of follicular stimulating hormone (FSH) between men with melasma (6.33 ± 0.96 U/L) and controls (4.11 ± 0.84 U/L). The LH/FSH ratio was 1.20 ± 0.21 in men with melasma and 2.02 ± 0.64 in controls, with statistically insignificant difference. The mean circulating testosterone was significantly lower ($p < 0.002$) in men with melasma (11.97 ± 0.84 nmol/L) compared to the controls (20.51 ± 2.25 nmol/L). A significantly high level of circulating LH coupled with low levels of circulating testosterone with an LH/FSH ratio within the normal range suggests the presence of subtle testicular resistance in men with melasma. Similarly, presence of mild subclinical ovarian dysfunction has been reported in a study of 9 women with idiopathic melasma in whom a statistically significant increase in the levels of LH were found along with a lower levels of serum estradiol as compared to normal age and sex matched controls.[10]

CLINICAL FEATURES OF MELASMA IN MEN

The age range of melasma in men is between 18 and 72 years, with an average age of onset of 30.7 years[1,2,4] similar to female patients. In the first study group comprising of poultry workers in the study by Pichardo et al.[1] on Latino men, the prevalence of melasma was highest (70%) in men older than 31 years and was absent in men aged 18–24 years. In the rest of the two study groups of farm workers, melasma was prevalent across all the age groups, although its prevalence was highest in men older than 31 years. In concordance with this study, both the studies by Sarkar et al.[4,5] reported the mean age of melasma in men to be 33.5[5] years and 34.5[4] years (Table 3). Of the 41 men with melasma in the study by Sarkar et al.,[5] 21 (51.2%) men were in the age group of 31–40 years, 11 (26.8%) men were between 19 and 30 years, and 9 (22%) men were 41 years and older. However, in contrast to these findings, Vazquez et al.[2] observed a higher average age (38.8 years) of melasma in men. The range of age and the disease duration were similar between men and women with melasma (Table 2). The mean duration of melasma reported in Indian studies by Sarkar et al. are 1.4 years and 3.5 years in contrast to a longer duration of 8 years reported by Vazquez et al.[2,4,5] Another Indian study by Sialy et al. also reported a shorter duration of melasma ranging between 2 months to 1.5 years (Table 3).[8]

In the study by Vazquez et al.[2] and Sarkar et al.,[5] the clinical and histological characteristics of melasma in men were same as those for women barring hormonal factors which did not seem to play a significant role in men (Tables 2 and 3). In men, melasma is most commonly seen on the face, it can also involve the neck and forearms.

In men, malar type of melasma was the most common clinical pattern (44.1–61%) seen in majority of the studies (Table 3) compared to women in whom the centrofacial pattern was the most common (Table 2). The difference between the clinical pattern of melasma between men and women in the study by Sarkar et al.[5] was found to be statistically significant (Table 2).

In the study by Vazquez et al.,[2] associated diseases that were seen in men with melasma were acne in 2 patients, male pattern alopecia in four patients and chronic liver disease in 1 patient. Signs of hormonal disturbance like presence of gynecomastia, spider angiomata, obesity, striae, and palmar erythema were not observed in any of the patients. In the study by Sarkar et al.,[5] none of the patients gave history of any endocrinological disorder, parasitic infestations or any other systemic diseases. Similarly, none of the patients had any underlying systemic or endocrine disorder in the study by Sialy et al.[8]

Woods lamp examination of melasma revealed the epidermal pattern (uniform enhancement of the pigmented area) to be the most common in men across all the studies (48.4–68.3%) (Table 3), similar to women.[2,4,5]

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The histopathological patterns of melasma were similar in both men and women. In the study by Sarkar et al.,[5] histopathological analysis was done in 20 (48.8%) men with melasma and 40 (25%) women with melasma and the changes were similar in both men and women (Table 2). Epidermal pattern of melasma with increased melanin in both basal and suprabasal layers of the epidermis was the most common pattern seen in both men (50%) and women (62.5%). The dermal pattern with dendritic melanocytes and melanophages was the least common pattern seen in both men (5%) and women (7.5%). Additional histopathological features seen were solar elastosis in 17 (85%), flattening of rete ridges in 9 (45%), and infiltration by chronic inflammatory cells in 6 (30%) male patients with no evidence of basal layer degeneration. In accordance to this study, in the studies by Sarkar et al. and Vazquez et al., epidermal type of melasma was the predominant histopathological type seen in men (Table 3).[2,5] Jang et al.[7] compared the histopathologic characteristics of 8 men and 10 women with melasma. Men with melasma had increased vascularity. Men with melasma also had significantly increased lesional stem cell factor and c-kit expression. Also, the lesional to nonlesional ratio of stem cell factor and c-kit expression was increased in men with melasma compared to women with melasma. This suggests the role of chronic UV radiation associated with signaling of paracrine cytokines in the mechanism of melasma in male patients. As the epidermal variety of melasma is more amenable to treatment, melasma in men could be more responsive to treatment.

MELASMA AND QUALITY OF LIFE IN MEN

Though melasma is less commonly seen in men compared to women, nevertheless it can negatively affect the quality of life (QoL) in men. In the study by Pichardo et al.,[1] there was a statistically significant difference in the Dermatology Life Quality Index (DLQI) in men with and without melasma (7.5 vs. 2.8) in the group of poultry workers, indicating a poor QoL (Table 4). There was a moderate association with the QoL in men in the poultry worker group. However, there was no statistically significant difference in the DLQI between men with and without melasma in the other two groups of farm workers.

DIFFERENTIAL DIAGNOSIS

In men, the differential diagnosis of melasma includes freckles, solar lentigo, postinflammatory hyperpigmentation, nevus of Ota, nevus of Hori, pigmented contact dermatitis, lichen planus pigmentosus, frictional melanosis, facial acanthosis nigricans, and Becker's melanosis. These conditions may sometimes even coexist with melasma. A careful medial history should include age of onset, progression and history of chemical exposure. Clinical examination of the skin should include Wood's lamp examination, dermoscopy, and the recognition of concomitant inflammatory disorders. At times, histological findings are helpful in making the correct diagnosis.

Table 4: Dermatology Life Quality Index in men with melasma[1]

Study groups	Mean total DLQI in men with melasma	Mean total DLQI in men without melasma	Significance
Poultry worker study (n = 25)	7.5	2.8	0.02
Cross-sectional farm worker study (n = 54)	3.5	4	0.82
Longitudinal farm worker study (n = 300)	1.12	1.09	0.92

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TREATMENT

Some special considerations should be taken into account for treating melasma in men. The use of cosmetic camouflage (like using makeup in women) is generally not practical in men. Also men tend to avoid complex and time-consuming regimens and therefore simpler regimen is preferred. They also want a fast fix to their disease which will produce immediate visible improvement.[11] Unfortunately, there is still no "quick fix" for this condition. Hence, it is important to inform the patient regarding the length of the treatment. Over-correction and feminization should be avoided. Regarding the formulation, men prefer solution over cream or ointment.[6] However, sometimes the stinging sensation due to the presence of high ethanol content in the solution especially when applied after shaving can be problematic. The products chosen for treating melasma in men should not be heavily fragranced and should not have an overtly feminine packaging.[12] Efforts should be made to identify and remove the etiological factors and to instill sun protective behavior in the patients by encouraging the use of sunscreens, sun protective hats and clothing (for melasma present on arms). Treatment options include use of sunscreens, depigmenting creams, oral depigmenting agents, chemical peels, microdermabrasion, dermabrasion, mesotherapy, light and lasers, and platelet rich plasma therapy. Jang et al.[7] suggests that the key factor in prevention of male melasma is avoidance of sun exposure. Pharmacologic treatments form the mainstay of therapy. Some patients may respond to monotherapy and for those who do not, combinations of therapies should be used for optimizing the results. Broad-spectrum (UVA- and UVB-protective) sunscreens with a physical block (such as zinc oxide or titanium dioxide) with a minimum sun protection factor (SPF) of 30 should be applied daily and continued indefinitely. Sunscreens prevent melanocyte reactivation by sun exposure and broad-spectrum sunscreens may enhance the efficacy of hydroquinone as shown in a double-blind study.[13] However, men are less compliant with the use of sunscreen compared to women and therefore it is essential to emphasize the importance of use of sunscreen in men with melasma.[14] Topical depigmenting agents which are used alone or in combinations include hydroquinone, topical corticosteroid, retinoic acid, azelaic acid, kojic acid, arbutin, licorice extract, ascorbic acid and soy.[15] However, there is a scarcity of literature on treatment for melasma in men, probably because it is less common in men and also because men tend to rarely seek treatment for it. Keeling et al.[6] treated five men with melasma with a combination of 2% mequinol and 0.01% retinoic acid solution. Four patients achieved complete clearance and one patient showed moderate improvement in melasma at 12 weeks. According to the consensus of the Pigmentary Disorders Academy in the year 2006, topical therapy with fixed triple combinations should be the first-line of treatment for patients with melasma.[16] Monotherapies and dual therapies have lower efficacy and slower onset of action and are recommended if triple therapy is unavailable or in patients who have sensitivity to the ingredients. Glycolic acid (GA), salicylic acid, trichloroacetic acid (TCA), retinoic acid, and resorcinol are the chemical peels used for treating melasma.[17] Glycolic acid peels have modest benefit in melasma and a dose-response trial showed that 52.5% GA applied for 3 minutes results in clinical improvement, whereas a lower concentrations does not.[18] However, caution should be exercised in using peels in darker skin types, as it can cause irritation and postinflammatory hyperpigmentation. Laser and light treatment used for treating melasma include Q-switched neodymium:yttrium-aluminum-garnet (QS Nd:YAG) laser, Q-switched ruby laser, Q-switched alexandrite laser, copper bromide laser, erbium:YAG laser, 1,550 nm erbium-doped fractional laser, and intense pulsed light. Among these, the nonablative 1,550 nm fractional laser is United States Food and Drug Administration approved for the treatment of melasma.[19] A split faced, observer-blinded, randomized controlled study showed significant worsening of hyperpigmentation along with

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a high rate of postinflammatory hyperpigmentation (31%) in patients of melasma, however, the numbers of men with melasma in this study was limited.[20] Zhou et al.[21] evaluated the efficacy and safety of low energy (6-mm spot size, fluence of 2.5–3.4 J/cm^2, and frequency of 10 Hz) 1064 nm QS Nd:YAG laser performed weekly for nine sessions in 47 women and three men with melasma. Ten percent patients had complete clearance and 70% had more than 50% decrease in Melasma Area and Severity Index values. However, there was a high recurrence rate of 64% at the 3-month follow-up. There was no statistically significant association between the efficacy of QS Nd:YAG laser and sex. Similarly, in a study by Wattanakrai et al.,[22] the efficacy of low-fluence QS Nd:YAG laser was found to be similar in male and female patients with melasma. Although laser can produce rapid and significant results in some patients, recurrence is common and there is a risk of postinflammatory hyperpigmentation, mottled hypopigmentation and rebound hyperpigmentation. Given the cost, variable results, need for multiple sessions and potential risk of side effects, laser, and light are not considered as the first-line treatment for melasma in both men and women.

A split-face, investigator-blinded, randomized controlled study was conducted comparing low-fluence Q-switched Nd:YAG 1,064 nm laser (LFQS) monotherapy with a combination of LFQS and 30% GA peeling in 15 Thai male patients with mixed type melasma.[23] Patients received 5 sessions of LFQS (MedLite C6, 6-mm spot size collimated homogeneous flat-top beam profile, energy fluences of 2.2–2.8 J/cm^2 at 10 Hz) performed at weekly interval on one side of the face and LFQS plus 30% GA peeling on the other side of the face and were followed up for 12 weeks. Twelve patients completed the protocol. Objective evaluation of the results were done using the relative lightness index (RL*I). Subjective evaluation was done by 2 blinded independent dermatologists by scoring modified Melasma Area and Severity Index (mMASI). Patient's assessment of improvement in terms of percentage of improvement in melasma was documented at 4 and 12 weeks of follow-up and by using visual analog scale on the final visit. On the side where combination of LFQS and 30% GA peeling was done, there was a significant reduction in the baseline mean RL*I (8.20 $\pm$ 0.73) at week 2 (6.95 $\pm$ 0.64, $p = 0.029$) and it reached the lowest value (3.91 $\pm$ 0.5) at week 4 of follow-up ($p = 0.001$), representing 52.3% maximal improvement. On the side treated with laser monotherapy, the mean baseline RL*I (7.98 $\pm$ 0.73) showed similar trend but there was significant reduction at 4-weeks of follow-up (4.97 $\pm$ 0.54, $p = 0.001$), representing maximal improvement of 37.6%. Both the sides showed a transient increase in mean RL*I after 2 treatment sessions. Combined treatment showed a significantly lower mean RL*I at week 4 (4.35 $\pm$ 0.63 vs. 6.42 $\pm$ 0.63, $p = 0.023$) compared to the monotherapy treatment. There was a rebound increase in RL*I with both the treatments during the last 2 follow-ups. However, the combined treatment had a significantly lower mean RL*I than baseline ($p = 0.009$ at 8-week follow-up and $p = 0.005$ at 12 weeks follow-up). There was a significant reduction in the mean mMASI score on the combined treatment side since week 3 compared to the baseline (20.08 $\pm$ 1.99 vs. 15.83 $\pm$ 1.80, $p < 0.001$) and it continued to decrease with time and reached the lowest value at 4-week follow-up (13.00 $\pm$ 2.17, $p = 0.001$); achieving maximal improvement of 37.6%. On the laser monotherapy side, there was no statistically significant reduction of baseline mMASI score throughout the study. Optimal reduction from the baseline was seen at 4-week of follow-up (16.50 $\pm$ 2.17, $p = 0.58$), representing maximal improvement of 14.6%. Participants who rated their response to treatment as >75% clearance of melasma was 61.5% on the combined treatment side versus 15.4% on the laser monotherapy side at 4-week follow-up and 41.7% versus 0% at 12-weeks of follow-up. Visual analog scale of the overall patient satisfaction was 8.25 $\pm$ 1.26 in the combined treatment side and 6.52 $\pm$ 1.29 in the laser monotherapy side ($p = 0.03$). Burning and stinging were the most common adverse effects occurring on both the sides. One patients with Fitzpatrick skin type V developed hyperpigmentation on both sides,

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which spontaneously improved in 3 months. Another patient with Fitzpatrick skin type V developed guttate hypopigmentation on the background of hyperpigmentation on both sides with the hypopigmentation remaining unchanged. Therefore, this study demonstrated that although combination of 30% GA peeling with LFQS reduced melasma in Asian men, there was a high incidence of side effects, including guttate hypopigmentation, which was irreversible. The study suggested that a more favorable outcome could be achieved with this combination by reducing the laser fluence, frequency of treatment, and the adjunctive use of topical agents.

CONCLUSION

Melasma is definitely less common in men compared to women, although its prevalence is found to be high in Indian, Southeast Asian, and Latino men.[24] The clinicohistopathological characteristics of melasma are same in both men and women. Both men and women with melasma share the same etiological features except for the hormonal factors which play an important role in causing melasma in women and have little or no role in men. In men, exposure to sunlight and a positive family history were the most prominent aggravating factors. Clinically, malar pattern is the most common pattern seen in men compared to the centrofacial pattern in women. It negatively affects the QoL in men as it does in women and since the epidermal type of melasma is the predominant histopathological type seen in men, it could be more responsive to treatment. Since most of the studies on treatment for melasma were conducted in women, therefore, it is recommended that treatment modalities are same for both men and women with melasma except for the use of cosmetic camouflage by makeup which is not practical in men. Also simpler regimens, efficacy, onset of action, and formulation are issues which should be taken into account while selecting a treatment regimen.

Editor's Note

Melasma is more frequent in dark skinned males and those who spend a longer time outdoor in the sun.

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CHAPTER 15

Platelet Rich Plasma Therapy, Microneedling, and Mesotherapy for the Treatment of Melasma

Shilpa Garg

INTRODUCTION

Melasma is a common cause of hypermelanosis which is characterized by hyperpigmented macules located on photo-exposed areas and primarily affecting women of childbearing age. Despite the wide therapeutic arsenal ranging from new to old topical and oral depigmenting agents and technologies like chemical peeling and lights and lasers, clinical control of this hypermelanosis is extremely challenging and the patient is rarely free of melasma for a long time. This chapter discusses certain newer therapies like platelet rich plasma therapy, microneedling, and mesotherapy in the treatment of melasma.

PLATELET RICH PLASMA THERAPY IN MELASMA

Platelet-rich plasma (PRP) therapy involves injection of high concentration of autologous platelets in a small volume of plasma. This therapy has been commonly used in dermatology for the treatment of chronic nonhealing ulcers, skin rejuvenation, acne scars, and, alopecia.[1] The α-granules present in platelets contain greater than 30 bioactive substances including platelet-derived growth factor, transforming growth factor β1 and 2, epidermal growth factor, platelet-derived angiogenesis factor, and fibrinogen.[2] Kim et al. have reported significant inhibition of melanin synthesis by transforming growth factor-β1 via delayed extracellular signal-regulated kinase activation.[3] It is possible that improvement in pigmentation seen after PRP therapy may be due to increase in skin volume (blood vessel formation and synthesis of collagen and hyaluronic acid) caused by platelet-derived growth factor. Although there are no controlled clinical trials on role of PRP in management of melasma, Cayirli et al. reported a case of regression of melasma with PRP therapy.[4] A 27-year-old woman with melasma of about 5 years duration was treated with three sessions of PRP with 15-day interval between the sessions. In each session, her face was injected with approximately 1.5 mL of PRP into the papillary dermis (1.5–2.0 mm deep) with a 32-gauge needle with superficial microinjections via the mesotherapy technique. At the end of the third session >80% reduction in epidermal hyperpigmentation was present. Patient was only given sunscreen for application along with PRP treatment. There was no recurrence reported in the follow-up period of 6 months.

The author herself has also found PRP to be useful in the treatment of melasma. The author has treated two patients of melasma who were resistant to standard modalities of treatment. Both the women underwent PRP therapy for the treatment of melasma. The Melasma Area Severity Index (MASI) score was 64 in the first patient and 47 in the second patient before starting PRP therapy. The MASI score post-6 sessions of PRP injections came down from 64 to 34 in the first patient and from 47 to 17 in the second patient. Although no controlled clinical trials are available at this point for the treatment of melasma with PRP, the author has found it to be very useful in her two cases that were treated with this modality.

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MICRONEEDLING FOR MELASMA

Microneedling also called as percutaneous collagen induction or derma roller is performed by rolling an instrument made up of a sterile plastic cylinder on which stainless steel needles are symmetrically aligned in rows. Microneedling creates thousands of microchannels through the epidermis into the papillary dermis leading to a confluent zone of superficial bleeding which acts as a stimulus for wound healing. Microneedling is commonly used for the treatment of acne scars. It also acts as a channel for enhancing drug delivery through the multiple microchannels that it creates in the skin. Since there is no epidermal ablation, this procedure carries minimal risk of postinflammatory hyperpigmentation or hypopigmentation. Although microneedling is more commonly used for enhancing the drug delivery of pigment reducing agents in melasma, its isolated action on improving melasma has been reported by Lima.[5] Lima conducted a study on microneedling on 22 patients (18 women and 4 men) with recalcitrant facial melasma who were unresponsive to topical lightening agents. Microneedling (1.5 mm size) was done under topical anesthesia using back and forth movements approximately 10 times in four directions leading to diffuse erythema and discrete punctuated bleeding. No active topical medication was used while doing microneedling. Along with microneedling patients were instructed to use triple combination cream (0.05% tretinoin + 4% hydroquinone + 1% fluocinolone acetonide) at night along with a sunscreen with SPF 60. The patients underwent a total of two sessions of microneedling performed one month apart. All the 22 patients reported satisfaction with the results and the author reported the result from good to very good on a scale of very good, good, reasonable, and poor.

MESOTHERAPY WITH TRANEXAMIC ACID FOR THE TREATMENT OF MELASMA

Topical trans-4-aminomethylcyclohexanecarboxylic acid (tranexamic acid) is a plasmin inhibitor which prevents ultraviolet-induced pigmentation by preventing the binding of plasminogen to keratinocytes resulting in decreased free arachidonic acids and diminished prostaglandins, which cause decrease in melanocyte tyrosinase activity.[6] Mesotherapy consists of intradermal or subcutaneous injection of 0.05–0.1 mL of a highly diluted single product or drug mixture at the site of aesthetic problem. All intravenously injectable substances can be given through mesotherapy except for oily and alcohol containing solvents. Mesotherapy allows direct delivery of adequate quantity of medication at the site of problem and avoids oral medications. The delivery of the drug directly at the site of concern also allows for lower dosages of drugs to be used. Lee JH et al. conducted a study on mesotherapy with tranexamic acid in the treatment of melasma in 100 Asian patients.[7] After applying topical anesthesia, 0.05 mL tranexamic acid (4 mg/mL) was injected intradermally using 30-gauge needle 1 cm apart into the area of melasma. The technique was repeated at weekly intervals for 12 weeks. Among the 85 patients who completed the study, there was statistically significant decrease in the MASI score at 8 and 12 weeks (p value = 0.05). According to the patients, 86% of them considered the results as "good or fair" improvement. All the patients felt immediate burning sensation and a mild wheal at the site of injection which resolved within 10 minutes. No significant side effects were noted. Sharma et al.[8] conducted a randomized controlled trail to compare the efficacy of oral and microinjections of tranexamic acid in the treatment of melasma. Out of the total 100 patients with melasma (8 men, 92 women, age range 18–55 years), 50 patients in group A (3 men, 47 women) received oral tranexamic acid 250 mg twice a day, while the other 50 patients in group B (5 men, 45 women) received intradermal microinjections of tranexamic acid (4 mg/mL) at an interval of 4 weeks. Both the groups were treated for 12 weeks. The percentage of reduction in MASI was assessed

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at 4 week intervals, and the response was graded as very good (>75% reduction), good (50% to <75% reduction), moderate (25% to <50% reduction), mild (<25% reduction), or no response. Thirty-nine patients in group A and 41 patients in group B completed the study. Twenty-five patients in group A and 32 patients of group B experienced very good response to treatment, respectively, while good response was seen in 14 patients of group A and 9 patients in group B, respectively. Treatment with both oral as well as microinjections with tranexamic acid were equally effective, with an average reduction of MASI score at 12 weeks of 77.96 ± 9.39 in group A and 79.00 ± 9.64 in group B. The authors concluded that tranexamic acid was an effective and safe treatment for melasma, irrespective of its route of administration.

Editor's Note

Physical therapies in melasma,except for peels and lasers,do not have much evidence at present,more so in dark skinned patients.However, there is a lot of interest in these and combining them with other modalities of treatment will help in improving outcomes in melasma in the future. However, we need to be cautious at present.

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CHAPTER 16

Treatment of Melasma: Future Directions

Anuva Bansal, Pallavi Ailawadi, Rashmi Sarkar

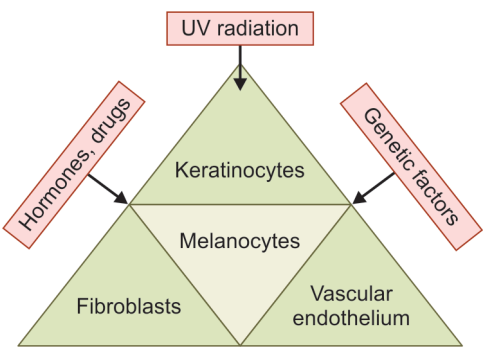
INTRODUCTION

Melasma is a common, acquired, symmetrical hypermelanosis, which is often difficult to treat and has a significant negative impact on patients' quality of life. The most commonly implicated etiological factors include genetic predisposition, ultraviolet radiation (UVR) and hormonal influence.

Melasma has been classically described as a linear model and classified on the basis of presence of localization of melanosomes in the skin as epidermal, dermal, and mixed.[1] However, with the use of newer modalities such as *in vivo* reflectance confocal microscopy, it has been discovered that the distribution of melanophages is heterogeneous and perhaps, suggests that all melasma is in fact 'mixed'. Further, changes such as increased solar elastosis and vascular proliferation suggest a significant involvement of the dermis in melasma.[2] Melasma is now being learnt as a complex interplay amongst the epidermal melanocytes, keratinocytes, dermal fibroblasts, mast cells, and vascular endothelial cells[2] (Fig. 1). The elaboration of this new concept has unlocked several other potential targets for research and treatment in the field of melasma.

MELANOGENESIS AND ITS REGULATION

Melanogenesis refers to the production of the melanin by melanocytes which are present in the skin surrounded by keratinocytes to which they transfer the synthesized melanin. Melanocytes contain melanosomes, where melanin is synthesized through a series of steps catalyzed by various enzymes like tyrosinase, tyrosinase related protein 1 (TYRP1), TYRP2 and the production of these enzymes is driven by the microphthalmia associated transcription



UV, ultraviolet.

Figure 1: Melasma–pathogenesis: A complex interaction among epidermal and dermal entities.

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factor (MITF).[3] The salient steps of this pathway are elucidated in Figure 2. The eumelanin to pheomelanin ratio contributes to skin pigmentation with a higher amount eumelanin leading to a darker skin phenotype. TYRP1, TYRP2, and the activation of melanocortin 1 receptor (MC1R) by the melanocyte stimulating hormone (α-MSH) or adrenocorticotropic hormone (ACTH) induce a switch from the production of pheomelanin to eumelanin synthesis.[4] Further, there is an upregulation of genes involved in melanogenesis in the lesional skin of melasma patients and these melanocytes are found to be more biologically active with more dendrites, mitochondria, golgi bodies, and rough endoplasmic reticulum suggesting that an increased biological activity rather than an increased number of cells is responsible for hyperpigmentation in melasma.[5]

Thus, agents inhibiting the activity of melanocytes rather than melanin synthesis alone would be more effective than the conventional agents.

Newer Agents Targeting Melanogenesis and Hyperactive Melanocytes (Fig. 3)

Conventional agents such as hydroquinone and azelaic acid have been demonstrated to exert their effects selectively in hyperactivated melanocytes that is those cells that have an active tyrosinase activity.[6]

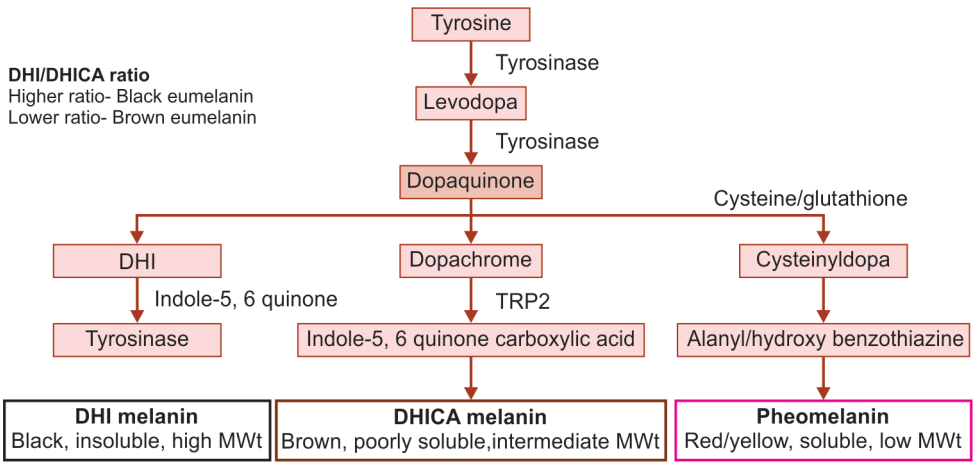
Newer agents specifically targeting hyperactive melanocytes include the following.

Linoleic Acid

It has a significant lightening effect in ultraviolet B (UVB) induced pigmentation and selectively targets tyrosinase in hyperactive melanocytes.[7]

Ascorbic Acid

It reduces dopaquinone and DHICA oxidation. However, it is highly unstable and has decreased penetration into the skin. Esters of ascorbic acid such as magnesium-l-ascorbyl-2-phosphate (VG-PMG) have been found to be stable in water and are better absorbed. They have been shown to induce a lightening effect in normal as well as hyperactive melanocytes.[8]



DHI, dihydroxyindole; DHICA, dihydroxyindole-2-carboxylic acid; L-DOPA, L-3,4-dihydroxyphenylalanine; TRP2, tyrosinase-related protein 2; MWt, molecular weight

Figure 2: Pathway of melanogenesis and the role of the dihydroxyindole/5,6-dihydroxyindole-2-carboxylic acid ratio.

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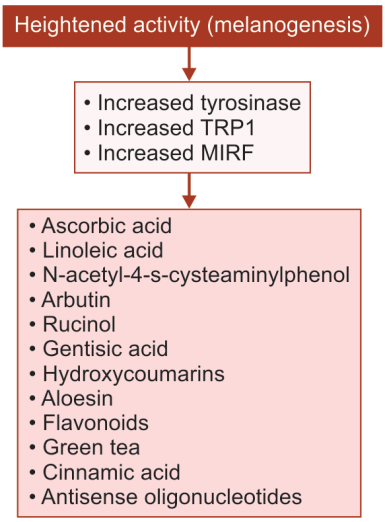

TRP1, tyrosinase-related protein 1; MITF, micropthalmia associated transcription factor

Figure 3: Drugs acting on the hyperactive melanocytes and melanogenesis.

N-acetyl-4-S-cysteaminylphenol

N-acetyl-4-S-cysteaminylphenol is a phenolic compound effective in the treatment of melasma. In comparison with hydroquinone (HQ), it is more stable and causes less irritation. It inhibits tyrosinase especially among hyperactive melanocytes, decreases intracellular glutathione by interfering with the thiol system, and favors the pathway of pheomelanin at the expense of eumelanin formation.[9]
Newer agents targeting melanogenesis include the following.

Arbutin

Arbutin the β-D-glucopyranoside derivative of HQ is derived from the leaves of different plant species including bearberry, blueberry, cranberry, and pear trees.[10] Apart from being a competitive inhibitor of tyrosinase it also inhibits tyrosine hydroxylase and DOPA-oxidase as well as melanosome maturation. The action of arbutin is dose-dependent and less toxic than HQ.[11]

Deoxyarbutin

Deoxyarbutin is a derivative of arbutin and is effective in reversible skin lightening by the direct inhibition of tyrosinase.[11] However, it has less melanocyte cytotoxicity as compared to arbutin and HQ.[10]

Aloesin

Aloesin is a compound, isolated from *Aloe vera* and it competitively inhibits the hydroxylation of tyrosinase to DOPA and the oxidation of DOPA to the dopachrome.[10] The application of aloesin four times a day for 15 days on the volar aspect of UV-irradiated human forearm showed dose-dependent inhibition of pigmentation.[12] A combination of aloesin and arbutin synergistically inhibit melanin synthesis by the combined action of non-competitive and competitive tyrosinase inhibition.[13]

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Rucinol

It is a phenol derivative that inhibits tyrosinase and TYRP-1. 4-N-butylresorcinol 0.1% cream showed rapid efficacy and safety in the treatment of melasma in a randomized, double-blind, vehicle-controlled, split-face comparative study done in 20 patients.[14]

Flavonoids

Flavonoids are benzopyrene derivatives which are competitive inhibitors of tyrosinase. Further, they also possess significant anti-inflammatory and antioxidant activity.[10] Trihydroxyisoflavone causes significant tyrosinase inhibition and is considered to be more potent than kojic acid (KA). Hesperidin is another flavonoid which also provides protection against UV radiation and free radical induced damage.

Epigallocatechin Gallate

Epigallocatechin gallate, a phenolic compound is obtained from green tea. It has been found to inhibit melanin production in a dose-dependent manner and also possesses anti-inflammatory, antioxidant, and anticarcinogenic properties.[9]

Ellagic Acid

It is a polyphenol that is found in green tea, strawberries, and pomegranate extract. It acts by inhibition of the proliferation of melanocytes as well as tyrosinase inhibition in melanocytes.[10]

Gentisic Acid

It is derived from gentian roots, and inhibits melanogenesis without any cytotoxic effects.[9,10]

Hydroxycoumarins

Hydroxycoumarins are natural lactones which are potent antioxidants and inhibit tyrosinase.[10] Umbelliferone or 7-hydroxycoumarin belongs to the Apiaceae (Umbelliferae) family which has additional anti-inflammatory properties.

Cinnamic Acid

Cinnamic acid a derivative of ginseng inhibits the tyrosinase activity[9] and in comparison to HQ, this agent is considered to be more potent.[15]

Antisense Oligonucleotides

Antisense oligonucleotides are effective in the treatment of melasma through modulating the synthesis of key enzymes of melanogenesis, including the tyrosinase, TRP1, and TRP2 by interacting with targeted mRNA at translational level. Additionally, it has been demonstrated that these agents act via decreasing the enzyme activity of DOPA oxidase.[10]

Role of Inflammation and Reactive Oxygen Species

Our skin experiences oxidative stress due to continuous exposure to several environmental stimuli, most important of which is UV radiation. Free radicals interact with the cellular lipids, proteins, DNA, carbohydrates, and enzymes, thus affecting the cellular function in its entirety. There are several antioxidant defense systems in place to prevent ROS associated tissue damage and a disrupted oxidant-antioxidant balance exists in melasma patients.

The reactive oxygen species (ROS) induce melanin synthesis by activating tyrosinase which prefers the superoxide anion radical [O_2^-] over O_2 as well as the direct photo-oxidation of the already synthesized melanin.[10] Multiple inflammatory mediators like interleukins C4, D4, IL-1, IL-6, and prostaglandin E2 stimulate melanocyte cell growth and

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dendrite proliferation, increase melanin production, and also damage the melanocytes, resulting in aberrant transfer of melanosomes into the dermis. Consequently, antioxidants and anti-inflammatory agents alone, or in combination with conventional drugs are being looked upon as potential therapeutic modalities in melasma.

Newer Agents Targeting Reactive Oxygen Species and Inflammation (Fig. 4)

Liquorice Extract

It is derived from the root of *Glycyrrhiza glabra*, liquorice extract disperses melanin, inhibits melanin biosynthesis and decreases ROS.[9] Furthermore, it has been found to possess anti-inflammatory action via the inhibition of the superoxide anion and cyclooxygenase.[16] It has been shown to significantly decrease UVB irradiation induced hyperpigmentation in guinea pigs when applied for 3 weeks.

Proanthocyanidin

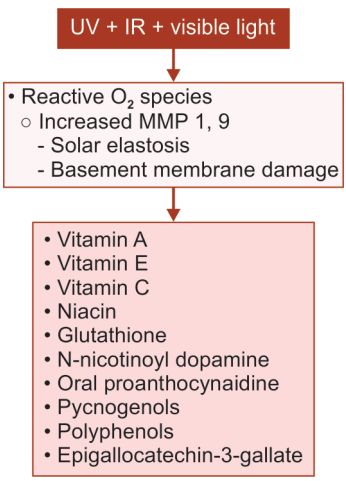
It is a powerful antioxidant that is extracted from grape seed and has been found to be efficacious in melasma in various studies.[9] Proanthocyanidin-rich grape seed extract (GSE) was orally administered to 12 Japanese woman and the first 6 months of GSE intake improved or slightly improved chloasma in 10 of the 12 women (83%, $p < 0.01$).[17]

Acidified Amino Acid Peels

These are potent antioxidants with significant tyrosinase inhibitory activity with a pH closer to that of skin, thus possessing a better side effect profile than glycolic acid.[18]

Orchid Extract

It has significant antioxidant activity and its efficacy has been found to be similar to vitamin C in melasma as shown by a study comparing orchid extract to 3% vitamin C derivative in 48 female patients.[9]



UV, ultraviolet; IR, infrared; O_2, oxygen; MMP, matrix metalloproteinase.

Figure 4: Role of drugs with antioxidant and anti-inflammatory activity.

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Coffeeberry Extract

It has antioxidant properties and its usage was found to significantly reduce hyperpigmentation and photo damage in 40 patients of melasma, when applied for 6 weeks.[9]

Mulberry Extract

It is derived from the plant *Morus alba* L and it causes tyrosinase inhibition and has superoxide scavenging activity. The concentration causing 50% inhibition tyrosinase activity is lower (0.396%) as compared to 5.5% for HQ and 10.0% for KA. In a randomized vehicle controlled trial of 50 patients of melasma, it caused significant improvement in melasma area and severity index (MASI) score.[9]

Pycnogenol

It is derived from the bark of *Pinus pinaster* and contains procyanidins, polyphenolic monomers, phenolic, or cinnamic acids. It has significant antioxidant and anti-inflammatory properties. Oral pycnogenol has been found to be efficacious in melasma.[9]

Other Agents

Flavonoids, epigallocatechin, hydroxycoumarins, and *polypodium leucomatous* extract are among the newer botanical agents which primarily act via melanogenesis inhibition as mentioned above but are strong antioxidants with a prominent anti-inflammatory action.[9,10]

Ascorbic acid or vitamin C, α-tocopherol or vitamin E as well as zinc in topical and oral formulations are known to be effective agents because of their prominent antioxidant and anti-inflammatory action.[9] Topical methimazole which is a potent peroxidase inhibitor can be use in treating melasma.[10] SMA-432 is a prostaglandin E2 inhibitor which has been used in treating melasma successfully.[10]

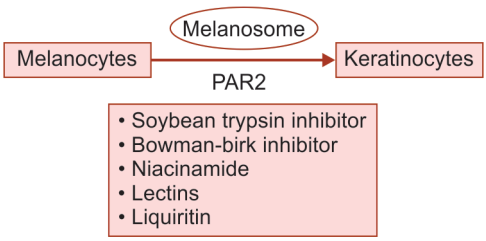
MELANOSOMAL TRANSFER: PROTEASE-ACTIVATED-RECEPTORS 2 RECEPTORS

Once the melanosomes are formed in the epidermal melanocytes, they are transferred to the neighbouring keratinocytes. Some whitening agents such as niacinamide, soybean, and soymilk extracts prevent the melanosome transfer by inhibiting the keratinocyte (PAR-2).[10]

Newer Agents Targeting Melanosomal Transfer (Fig. 5)

Niacinamide

Niacinamide or vitamin B_3 is the physiologically active amide of niacin found in the yeast and root vegetables.[10] It modulates PAR2, subsequently interfering with the transfer of melanosomes from melanocytes to surrounding keratinocytes.[9,10]



PAR2, protease activated receptor 2.

Figure 5: Role of drugs inhibiting the melanosomal transfer to keratinocytes.

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Soymilk, Soybean

Genistein and diadzein are primary metabolites of soy and have the active ingredients, soy trypsin inhibitor and Bowman-Birk inhibitor which inhibit PAR2 activation and possess antioxidant activity.[9] A double-blind study of soy-containing moisturizer with a broad-spectrum sunscreen in 68 patients over 3 months demonstrated significant improvements in rhytides and hyperpigmentation.[10]

Liquirtin

It induces skin lightening by dispersing melanin and studies demonstrate that a 20% liquiritin cream applied at 1 g/day for 4 weeks is therapeutically effective in melasma.[19]

THE DEFECTIVE SKIN BARRIER IN MELASMA

Melasma skin is characterized by impaired stratum corneum integrity and a delayed barrier recovery rate. Recently, it has been found that genes associated with lipid metabolism were downregulated in melasma, both de novo and chronic UV damaged induced. The lower synthesis of epidermal free fatty acids (FFA) and triglycerides results in an altered skin barrier.[20] Epidermal changes are important in the melanogenesis because there is a potential cross-talk between keratinocytes and melanocytes for pigmentation in response to stress to the barrier. Also downregulation of several lipid metabolism-associated genes such as peroxisome proliferator-activated receptor alpha (PPAR-α) leads to barrier damage in melasma. Some of the agents which act on these steps are as follows.

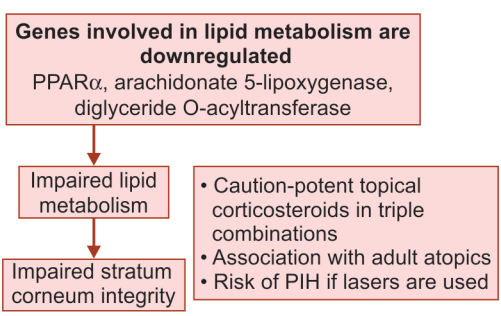
Newer Agents Targeting the Defective Barrier (Fig. 6)

Soy

It has been shown to reduce UVB induced pigmentation.[9]

THE VASCULAR COMPONENT

Increased dermal vascularity and expression of angiogenic factors seem to play a role in melasma, and have remained important areas of interest in pigment research. Increased number and size of vessels has been found in the lesional skin in melasma probably as a result of increased production of angiogenic factors such as vascular endothelial growth factor (VEGF) which could have a direct influence on melanocyte behavior through its receptor on them.[21] These blood vessels or endothelial cells modified by UV radiation release cytokines



PIH, postinflammatory hyperpigmentation; PPAR-α, peroxisome proliferator-activated receptor alpha.

Figure 6: Role of a defective skin barrier in melasma.

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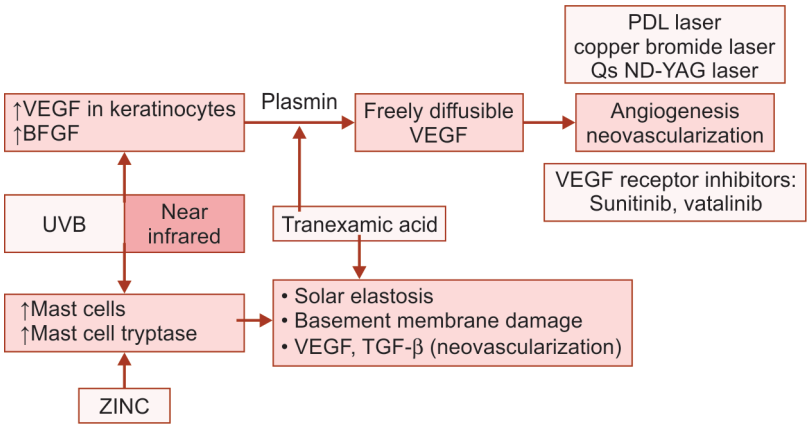

VEGF, vascular endothelial growth factor; BFGF, basic fibroblast growth factor; PDL, pulsed dye laser; ND-YAG, neodymium-doped yttrium aluminum garnet; UVB, ultraviolet B; TGF-ß, transforming growth factor beta.

Figure 7: Role of the vascular endothelium and mast cells**:** Tranexamic acid inhibits the plasminogen pathway as well as decreases the activity of mast cells. Zinc primarily affects mast cell degranulation.

and soluble factors like plasminogen which might be a possible cause of hyperpigmentation in melasma.

Newer Agents Targeting the Vascular Component (Fig. 7)

Tranexamic Acid

Tranexamic acid inhibits the plasmin/plasminogen pathway preventing the interaction between melanocytes and keratinocytes thus inhibiting melanogenesis.

Both oral and topical tranexamic acid have been found to decrease epidermal as well as dermal pigmentation and have also been found to reverse other dermal changes associated with melasma such as decreasing the number of vessels resulting in a visible reduction in the erythema and pigmentation.[22] Various studies have reported response rates of up to 89.7%, with the first signs of visible lightening observed at around 2 months after the intake of oral tranexamic acid. In an Indian study by Padhi et al. oral tranexamic acid was added to a conventional fluocinolone-based triple combination cream and faster reduction was seen in the tranexamic acid group compared to cream used alone.[23]

ROLE OF HISTAMINE AND THE MAST CELLS

Dermal mast cells have been found to be increased in the lesional skin in melasma. There is an increased production of histamine by these mast cells in response to UV radiation and this stimulates proliferation of melanocytes via H2 receptors. UV radiation also promotes the activation of mast cell tryptase which leads to extracellular matrix degradation as well as basement membrane disruption via elastin, matrix metalloproteinase (MMP) and a protease-granzyme B.[24] Furthermore, mast cells also produce vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and fibroblast growth factor (FGF-2) which promote angiogenesis and vascular proliferation contributing to the hyperpigmentation.

Despite the proposed role of mast cells in its pathogenesis, anti-histamines have still not found a place amidst the vast line of agents targeting melasma.

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Newer Agents Targeting Mast Cells (Fig. 7)

Tranexamic Acid

Tranexamic acid has been found to decrease the activity of mast cells. In a study done by Na et al. 25 women with melasma consumed two transexamic acid tablets three times a day and applied a transexamic acid topical agent twice a day for 8 weeks. Skin biopsies were collected from eight subjects before and 8 weeks after treatment and on histopathological analysis, the number of mast cells were found to be decreased after transexamic acid treatment suggesting that the effect of transexamic acid in melasma, may in be part due to the effect on dermal mast cells.[22]

Zinc

Zinc also inhibits mast cell degranulation and thereby reduces the secretion of histamine.[25]

ROLE OF THE ESTROGEN RECEPTOR

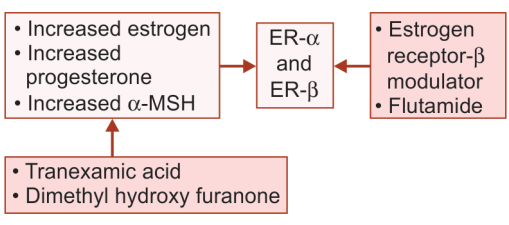
Melasma commonly develops in women of the reproductive age group and often occurs during pregnancy or amongst women consuming oral contraceptives establishing the role of hormones in the causation of melasma. Increased estrogen receptor expression has been found in the melasma lesional skin as compared to the adjacent normal skin, further validating the role of this hormone in hyperpigmentation.[26] Estrogens stimulate melanogenesis via synthesis of enzymes involved in melanin production such as tyrosinase, TRP-1, TRP-2, and MITF.[27] Inhibition of estrogen via its antagonist has been found to reduce melanogenesis.[27] The antiestrogen could be either a selective estrogen receptor modulator (such as tamoxifen or raloxifene) or an aromatase inhibitor (such as anastrozole or letrozole or exemestane).[28]

A novel topical agent having antiestrogenic activity has been proposed as a potential target for the treatment of melasma. Furthermore, studies suggesting that the 'triple therapy of the future' could now include a hydroquinone, an antiestrogen and a VEGF inhibitor.[28]

Newer Agents Targeting the Hormones (Fig. 8)

Topical Flutamide

Flutamide as an anti-androgenic agent may theoretically be considered to have an effect in treating melasma and in a parallel randomized clinical trial, amongst 74 women with melasma, patients received either a sunscreen along with 4% HQ cream or 1% flutamide cream. The following parameters were assessed: MASI score, mexameter melanin assay, and patient satisfaction. The study found that topical flutamide was as effective as topical hydroquinone in treating melasma but had a higher MASI, as well as a higher patient satisfaction level.[29]



α-MSH, alpha-Melanocyte-stimulating hormone; ER, estrogen receptor.

Figure 8: Role of the hormonal factors: Tranexamic acid affects α-MSH, while selective estrogen receptor modulators and flutamide inhibit the effect of estrogen.

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Flutamide may be efficacious in melasma via its effect on alpha-melanocyte-stimulating hormone or cyclic adenosine monophosphate which are the key regulators of melanin synthesis.

CONCLUSION

As the pathogenesis of melasma slowly unravels, newer therapeutic targets become available, opening the doors for putting to test the existing compounds as well as for developing newer molecules for treatment.

With the older concepts of a static process behind this entity being put to rest, we realize that melasma is in fact a complex epidermal-dermal interaction with the melanocytes, keratinocytes, blood vessels, and mast cells, all significantly, if not equally contributing to this dynamic process with inflammation, photo damage and reactive oxygen species further aggravating the problem. With this realization, it is now apparent that targeting the epidermal melanin alone will therefore not suffice.

This brings into picture agents targeting the hyperactive pendulous melanocytes, those possessing an anti-inflammatory oxygen scavenging action, those targeting the melanosomal transfer, as well as drugs acting on the vasculature, the hormonal receptors, and the defective skin barrier.

The list of the agents available today as potential targets for the treatment of melasma is growing day-by-day, and the equation in the future will most likely be governed by the side effect profile and the long-term safety of these drugs considering that melasma is mostly chronic and may be unyielding.

This necessitates long-term studies aiming to reach consensus regarding the 'ideal' agent for the treatment of melasma.

Editor's Note

Novel drugs targetting oxidative stress,oestrogen receptors,vascular factors and defective barrier function in melasma, are the ones for the future. Sunscreens protecting from infra red radiation also need to be studied in the future.The search for the perfect drug is still elusive although hope prevails in the horizon.

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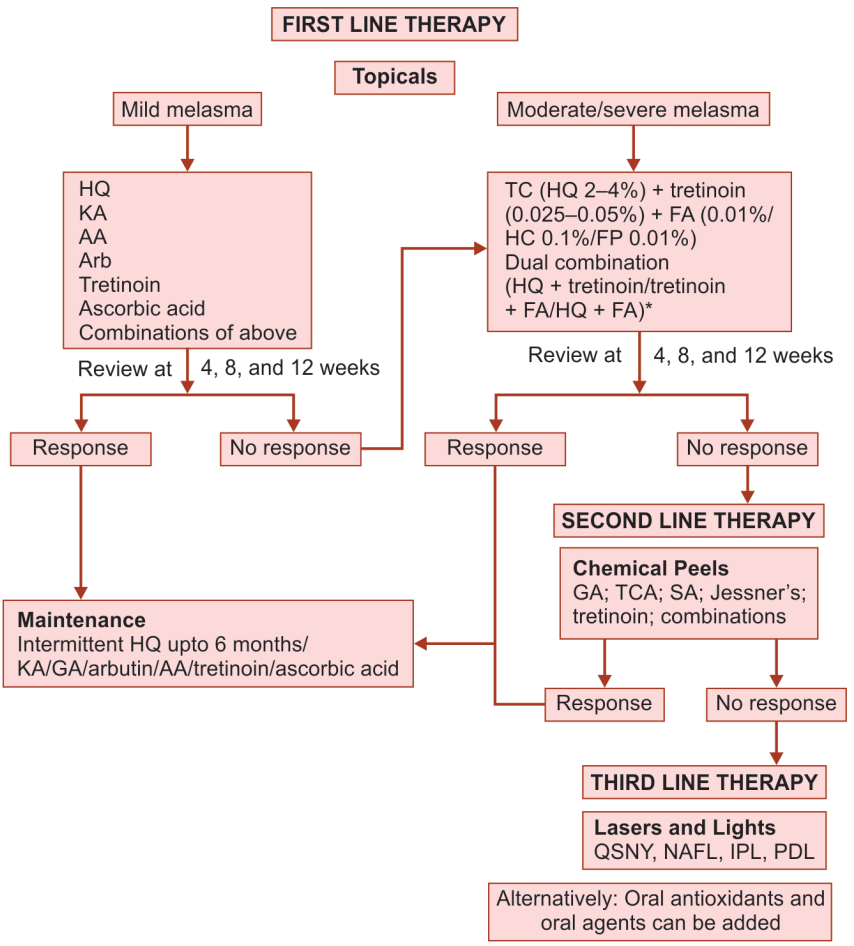
Treatment Algorithm for Melasma

Assess clinically and with Wood's Lamp (wherever possible). Treat any triggering medical factor.

Photoprotection: Broad spectrum sunscreen (Min PA+++, with inorganic sunscreens—TiO_2 or ZnO); Physical barrier



*To stop treatment anytime ochronosis is detected or side effects of topical steroids are detected.

TC, triple combination or modified Kligman's regime; FA, fluocinolone acetonide; FP, fluticasone propionate; HQ, hydroquinone; KA, kojic acid; AA, azelaic acid; Arb, arbutin; GA, glycolic acid; TCA, trichloroacetic acid; SA, salicylic acid; QSNY, Q-switched Nd:YAG laser; NAFL, non-ablative fractional laser; IPL, intense pulse light; PDL, pulsed dye laser.

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