Powering Through Pigmentary Disorders

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose
Objectives

• Review some of the common pigmentary disorders
• Review diagnostic tools available in the diagnosis and management of these disorders
• Discuss patient and treatment selection to maximize benefits and limit potential side effects
Skin Color

• **Constituitive**
  - Polygenic (MCIR, TYR, P)
  - Melanin quantity/distribution
  - Eumelanin (brown-black) vs pheomelanin (yellow-red)
  - Blood flow (hemoglobin)
  - Beta Carotene (yellow)

• **Facultative**
  - Sexual dysmorphism
  - Geographic variation
  - Latitude changes, diet, body covering and shelter
# Skin Phototypes

<table>
<thead>
<tr>
<th>Eye colour</th>
<th>Do you turn brown?</th>
<th>Score</th>
<th>Skin Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Light colours</td>
<td>0. Never</td>
<td>0-6</td>
<td>Skin Type I (always burns, never tans (pale white skin))</td>
</tr>
<tr>
<td>1. Blue, gray or green</td>
<td>1. Seldom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Dark</td>
<td>2. Sometimes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Black</td>
<td>4. Always</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Natural hair colour</th>
<th>How brown do you get?</th>
<th>7-13</th>
<th>Skin Type II (always burns easily, tans minimally (white skin))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Sandy red</td>
<td>0. Never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Blond</td>
<td>1. Light tan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Chestnut or dark blond</td>
<td>2. Medium tan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Your skin colour (unexposed areas)</th>
<th>Is your face sensitive to the sun?</th>
<th>1-20</th>
<th>Skin Type III (burns moderately, tans uniformly (light brown skin))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Reddish</td>
<td>0. Very sensitive</td>
<td>21-27</td>
<td>Skin Type IV (burns minimally, always tans well (moderate brown skin))</td>
</tr>
<tr>
<td>1. Pale</td>
<td>1. Sensitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Beige or olive</td>
<td>2. Sometimes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Dark brown</td>
<td>4. Never have a problem</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Freckles (unexposed areas)</th>
<th>How often do you tan?</th>
<th>28-34</th>
<th>Skin Type V (rarely burns, tans profusely (dark brown skin))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Many</td>
<td>0. Never</td>
<td>35+</td>
<td>Skin Type VI (never burns, deeply pigmented dark brown to black skin)</td>
</tr>
<tr>
<td>1. Several</td>
<td>1. Seldom</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Few</td>
<td>2. Sometimes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Rare</td>
<td>3. Often</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. None</td>
<td>4. Always</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If you stay in the sun too long?</th>
<th>When was your last tan?</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Painful blisters, peeling</td>
<td>0. +3 months ago</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Mild blisters, peeling</td>
<td>1. 2 - 3 months ago</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Burn, mild peeling</td>
<td>2. 1 - 2 months ago</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Rare</td>
<td>3. Weeks ago</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. No burning</td>
<td>4. Days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The information published here is not intended to take the place of medical advice. Please seek advice from a qualified health care professional.
Melanosomes and Melanin Synthesis

- Racial differences NOT due to differences in number of melanocytes, but rather the size, distribution, and number of melanosomes (all races have SAME melanocyte density).

- Individuals with darker skin have higher total melanin content, and a higher amount of eumelanin than lighter-skinned individuals.

- Hyperpigmentation occurs because of a change in melanin production/degradation and/or its distribution.

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Table 65.3 Melanosomes in lightly pigmented versus darkly pigmented skin.

<table>
<thead>
<tr>
<th>Lightly pigmented skin</th>
<th>Darkly pigmented skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanization</td>
<td>Stages II, III</td>
</tr>
<tr>
<td>Size (diameter)</td>
<td>0.3–0.5 microns</td>
</tr>
<tr>
<td>Number per cell</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Distribution</td>
<td>Groups of 2–10</td>
</tr>
<tr>
<td>Degradation</td>
<td>Fast</td>
</tr>
</tbody>
</table>

Melanin Biosynthetic Pathway

```
Tyrosine → DOPA → DOPAquinone → Pheomelanin or Eumelanin
(yellow to red pigment) (brown-black pigment) (round lamellar melanosomes) (oval melanosomes)
```
Vitiligo

**Immuno-genetic factors**
- HLA, CTLA-4, PTPN22, NLRP1, FOXP3, TNFA, IL4, IFNG, IL10, TGF, TGFBR2, TAP1, AIRE, IL1RN

**T cells**
- Altered Treg cell function
- Anti-melanocyte CD4⁺ and CD8⁺ T cells
- Increase in Th17 cells
- Altered T cell cytokines profiles

**B cells**
- Anti-melanocyte autoantibody production

**Antigen presenting cells**
- MHC antigen variants
- Defective antigen processing and presentation
- Increased macrophage infiltration

**Triggering factors**
- Physical and chemical stresses
- Defective apoptosis
- Altered self-antigens
- Formation of neo-antigens
- Heat-shock proteins

**Generation of autoimmunity and vitiligo**
Vitiligo
Treatment Options

Antioxidants?
Melanocyte Stress

Topical Immunosuppressants
Autoimmune Destruction

Phototherapy

Surgery
Melanocyte Regeneration

CD8+ T CELL
Skin conditions similar to Vitiligo

- Piebaldism
- Pityriasis Alba
- Tinea versicolor
- Halo nevus
- Nevus anemicus
- White scars
Diagnosis

- Physical Examination
- Wood’s Lamp
- Potassium hydroxide (KOH) microscopic evaluation
- Fungal culture
Pityriasis Versicolor
Pityriasis Alba
Retrospective chart review to evaluate frequency of dermatologic d/o by race

- N=1173 (Skin of Color Center, NYC)
  - Black: 744
  - White: 429

- Dyschromia = #2 most common dx amongst black patients (not in top 10 of white)

Alexis et al, Cutis 2007
X-sectional study, n= 419

- DLQI surveys of patients with melasma, PIH, lentigines, seborrheic keratoses
- Poorest QOL scores PIH (DLQI 8.5) > melasma (DLQI 7.0)
  - Psoriasis patients with mean BSA 28% = average DLQI 12
  - Severe occupation hand eczema = average DLQI 7.8
- Higher in women, <35 yo
- QOL worse in darker skin types

Maymone et al, JAAD 2017
Feldman et al, JAAD 2005
Cvetkovski et al, BJD 2006
Where Is the Pigment?

• **Epidermal vs Dermal vs Mixed**
  – Epidermal pigmentation may be easier to target
  – Treatment options will vary depending on pigment location

• **Facial vs Non-Facial**
  – Treatment response and healing times will vary depending on body site involved
Photoaging-Related Dyschromia

- UV light, ranging from 280 to 400 nm,
- Visible light (VL) ranging from 400 to 700 nm
- Infrared light (IR) ranging from 700 to 2500 nm.

• Cutaneous Changes
  - Rhytides, lentigines, dyspigmentation, loss of elasticity and telangiectases
  - Involve facial and non-facial regions

• *Based on recent literature, UV radiation, VL, IR all induce pigmentation*

New FDA Rules About Sunscreen Labeling

The American Academy of Dermatology recommends consumers choose a sunscreen which states on the label:

- **SPF 30 OR HIGHER**
- **BROAD SPECTRUM**
- **WATER RESISTANT**

**SPF 30 or Higher**

Means a sunscreen protects the skin from ultraviolet A (UVA) and ultraviolet B (UVB) rays, both of which can cause cancer.

**BROAD SPECTRUM**

For up to 40 or 80 minutes, Sunscreen can no longer claim to be waterproof or sweatproof.

**WATER RESISTANT**

For up to 40 or 80 minutes, Sunscreen can no longer claim to be waterproof or sweatproof.

One ounce of sunscreen per application

One bottle (6 oz) of sunscreen should last only 6 applications

One ounce of sunscreen is enough to cover the exposed areas of the body.

Drug Facts

- **Actives Ingredients**
- **Purpose**
- **Sunscreen**

One ounce of sunscreen per application

One bottle (6 oz) of sunscreen should last only 6 applications
Common Triggers for Melasma

- Skin tone
- Increased estrogen hormones
- Pregnancy
- Sun exposure
- Skin inflammation
- Certain drugs
- Genetics
Vascular Changes in Melasma

- 50 Korean women with melasma
- Biopsy of lesional and perilesional skin
- Lesional skin:
  - ↑ vessel size and density
  - ↑ in vascular endothelial growth factor (VEGF) expression by keratinocytes
  - Number of vessels correlated with intensity of pigmentation

Many patients find camouflage makeup to be an important component in the treatment of their hyperpigmentation.

Several widely available brands come in a broad range of shades and offer heavy coverage to help even out skin tone:

- **Dermablend (Vichy Laboratories, Paris, France),**
- **Covermark/CM Beauty (CM Beauty, Northvale, NJ)**
- **Cover FX (Cover FX Skin Care; Toronto, Ontario, Canada)**
Melanin Synthesis

Tyrosinase

Tyrosine → Dopa → Dopaquinone

Leucodopachrome

Dopachrome

Dopachrome tautomerase

5,6 Hydroxyindole 2, carboxylic acid

2,6 Cysteinyl-dopa

5,6 Cysteinyl-dopa

Benzothiazine derivatives

Phaeomelanins

Quinones

Eumelanins

Tyrosinase related protein 1
Skin Lightening Agents

*Hydroquinone*

- Reduces conversion of dihydroxyphenylalanine to melanin by tyrosinase inhibition
- Resultant distorted melanosome formation, increased melanosome destruction and inhibition of DNA and RNA synthesis
- Available in 2% OTC and prescription formulations
- Highly reactive oxidative nature, with efficacy diminishing as discoloration progresses
Exogenous Ochronosis

- Associated with the prolonged use of skin-lightening products, most commonly those containing hydroquinone.
- Most commonly seen among the indigenous Black population in African countries and is thought to be due to localized homogentisic acid collecting within the dermis.
- Bluish, brown, and/or black mottled macules in areas where topical lightening agents have been applied.
- **Histology:** Yellow-brown banana-shaped deposits in the dermis.
- **Treatment:**
  - Stop the offending medication.
  - Can try medium depth peels or QS lasers or ablative lasers.


Active Products Against Melanin

- Prevent melanin synthesis
- Lower melanin synthesis
- Accelerate epidermal turnover to limit melanin transfer through melanosomes

- Tretinoin, tranexamic acid, other antiflammatory meds
- Azelaic acid, arbutine, licorice, HQ, kojic acid, vitamin C, phytic acid, resveratrol
- Arbutrin, glabridin, niacinamide, retinoids, linoleic acids
Retrospective analysis suggests that oral tranexamic acid may be a worthwhile adjunct in the treatment of refractory melasma.

A detailed history to exclude risk factors of thromboembolism, stroke, or heart disease is mandatory before initiating therapy.

<table>
<thead>
<tr>
<th>Superficial Depth Peel</th>
<th>Medium Depth Peel</th>
<th>Deep Peel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha hydroxy acid</td>
<td>Glycolic acid and TCA</td>
<td>Baker’s Gordon phenol, unoccluded</td>
</tr>
<tr>
<td>Modified Unna’s resorcinol paste</td>
<td>Jessner’s and TCA</td>
<td>Baker’s Gordon phenol, occluded</td>
</tr>
<tr>
<td>Jessner’s</td>
<td>Solid carbon dioxide and TCA</td>
<td></td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>TCA 50%</td>
<td></td>
</tr>
<tr>
<td>Solid carbon dioxide slush</td>
<td>Pyruvic acid</td>
<td></td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Full-strength phenol 88%</td>
<td></td>
</tr>
<tr>
<td>TCA 10%–25%; 35% variable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A Deceptively Simple Solution for Refractory Melasma: Glycolic Acid Peels and Hydroquinone at Home

Takanobu Mashiko, MD, * Aiko Oka, MD,† Ema Osawa, MD,* and Isao Koshima, MD

Macroscopic view of the right cheek of a 53-year-old woman with frictional melasma. A, After 2 months of tretinoin–hydroquinone therapy, skin pigmentation was poorly improved. B, After 2 months of modified treatment using 20% glycolic acid and 5% hydroquinone, the disease condition was dramatically improved.
Skin Needling to Enhance Depigmenting Serum Penetration in the Treatment of Melasma

G. Fabbrocini, ¹,*  V. De Vita, ¹  N. Fardella, ¹  F. Pastore, ¹  M. C. Annunziata, ¹  M. C. Mauriello, ¹  A. Monfrecola, ¹  and N. Cameli ²

UV digital photograph of 42-year-old woman at baseline

UV digital photograph of a 42-year-old woman treated by using skin needling with depigmenting serum (two months after the baseline).

Published online 2011 Apr
7. doi: 10.1155/2011/158241
Devices for Pigment Reduction

- Q-switched laser
- Picosecond laser
- Fractional laser
- Intense pulsed light laser
- Pulsed dye laser

Use with extreme caution
- Erbium laser
What’s the Problem?

High melanin content
+
Broad absorption of melanin

↓

Therapeutic challenges during laser treatment
Safely Treating Patients with Darker Skin Phototypes

• Goal:
  – Minimize Epidermal Pigment Absorption
  – Minimize Epidermal Irritation & Erythema ➔ PIH
  – Minimize Epidermal Heating ➔ blistering and scarring

• How to achieve that goal:
  – Longer wavelengths
  – Lower fluence
  – Longer pulse duration
For Darker Skin Phototypes...

- Less is more (Fluence, density, passes)
- Consider laser test site
- Stress need for strict photoprotection
- Discuss increased risk of PIH
- Consider pre-treatment use of retin-a or hydroquinone
- Use caution with ablative fractional devices
Results:
- Complete re-epithelialization in 24 hrs.
- Clear collagen denaturation from papillary dermis into mid reticular dermis
- Healing occurs from viable tissue. Zones of spared tissue contain clusters of epidermal stem cells and Transit Amplifyin

Courtesy of Chris Zachary, MD
Fractional Erbium-doped Yttrium aluminum garnet Laser-assisted Drug Delivery of Hydroquinone in the Treatment of Melasma

Figure 1 A 35-year-old female patient with a 4-year history of melasma: (A) before treatment with fractional Er:YAG laser + HQ cream, (B) clinical appearance 12 weeks after starting therapy, (C) before treatment with HQ cream alone, and (D) clinical appearance 12 weeks after starting therapy.

Figure 3 Dermoscopic photomicrographs of melasma lesions shows a fine brown reticular pattern superimposed on a background of faint light brown areas (original magnification X15): (A) at baseline, (B) 12 weeks after starting treatment with fractional Er:YAG laser + HQ cream, (C) at baseline, and (D) 12 weeks after starting treatment with HQ cream alone.
Optimal Wavelength

- **600nm – 1100nm**
  - selectively absorbed
- **Shorter wavelengths (694nm, 755 nm)**
  - higher melanin absorption
  - best for light skin color/light hair
- **Longer wavelengths (800nm, 1064nm)**
  - lower melanin absorption
  - best for darker skin color
Advancing Laser Treatments

**Q-switched Nd:YAG 1064nm laser:**
- Low fluence
- Combination therapy with pulsed dye laser

**Picosecond Nd:YAG 1064nm or Alex 755nm laser:**
- Low fluence
Post-inflammatory hyperpigmentation in a 20-year-old female. (A) Findings at baseline. (B) Findings after seven treatments of 5.25 J/cm$^2$ with a 2-mm spot size using a Picosecond 755-nm Alexandrite laser.

Laser Toning
Subcellular Selective Photothermolysis

- QS Nd:YAG 1064nm laser
- Low fluence (1.6-3.5J/cm²)
- Large spot size (4-8 mm spot size)
- Longer pulse duration (20ns)
- Multiple passes (2-4 passes)
- Repeat treatments every 1-2 weeks
- Melanin degradation and removal within melanocytes
- Melanocytes are left intact
- Photoacoustic effect
Clinical findings in a 43 year-old female patient (Patient No 19).  
a: Baseline condition.  
b: Findings 6 weeks after dual toning with the 1064 nm Nd:YAG laser, showing very good clearance of the melasma and improved general skin condition including reduced pore size and disappearance of the fine periocular lines.

doi: 10.5978/islsm.20.189
Laser Toning
Hypopigmentation/Depigmentation

• White round confetti-like macules
• Variable extent
• Appear more striking with surrounding melasma
• 8-10% risk
Pulsed Dye Laser Treatment

- **Melasma** – targeting vascular component
  - Longer pulse duration (10-20msec)
  - Larger spot size (10mm)
  - Fluence 7.5-8.5 J/cm; DCD 30/20
  - Consider combination treatment with fractionated laser

- **Lentigines**
  - Requires compression lens to purge tissue blood
  - Longer pulse duration
  - Conservative fluence; DCD 30/20

Geddes ER, Stout AB, Friedman PM
Pulsed Dye Laser Treatment of Post-Procedure Ecchymoses

Treatment Protocol
Energy density of 6J/cm², pulse duration 6ms, 10mm spot,
DCD 30ms spurt, 20ms delay
3 passes

Hydrogen Peroxide 40% Solution

- Applied in office
- Pen applicator
- Generally requires 1-2 treatments spaced 3 weeks apart
- Side effects include stinging, irritation, redness, blister, scar
- FDA approved
Periorbital Hyperpigmentation (Dark Circles)

Dark Circles
Combination Therapy

• **Tear Troughs**
  – Soft tissue augmentation

• **Pigmentation**
  – Q-switched and/or picosecond laser
  – Fractionated 1927nm non ablative laser

• **Vascularity**
  – Pulsed dye laser (telangiectases) and/or LP Nd:YAG1064nm laser (reticular veins)
Correction of Dark Circles

Fig. 13. Treatment of tear trough deformity with a double-crosslinked, nonparticulate hyaluronic acid filler. (Belotero Balance, Merz Aesthetics, Inc, Greensboro, NC.)

Fig. 5. Significant improvement in infraorbital hyperpigmentation after a single treatment with combination Q-switched 694 nm ruby laser (SINON, Alma Lasers Ltd, Buffalo Grove, IL) for hypermelanosis and long-pulsed 1064 nm Nd:YAG laser (CoolTouch VARIA, CoolTouch Inc, Roseville, CA) for reticular veins.

Treatment Success

- Consider biopsy if unclear diagnosis
- Ensure that underlying etiology is being managed to minimize the development of further pigmentary changes
- Consider treatment test site – must be performed in region of hyperpigmentation
What Does the Future Hold?

• Laser assisted drug delivery
• Combination therapies
• Gene modification therapies