Unmasking Facial Hyperpigmentation

Amit G. Pandya, M.D.
Professor
Department of Dermatology
University of Texas Southwestern Medical Center
Dallas, Texas, U.S.A.

Differential Diagnosis of Facial Hyperpigmentation

- Post-inflammatory hyperpigmentation
- Lentigines
- Melasma
- Periorbital dark circles
- Drug-induced hyperpigmentation
- Acanthosis nigricans
- Lichen planus pigmentosus
- Maturational hyperpigmentation
Melasma

- Common
- Affected by hormones - pregnancy and oral contraceptives
- May fade post-partum
- More common in brown races
- 90% are women
- Worsened by UVB and UVA light
- Psychologically distressing
- Distinct morphology

Visible Light and Melasma

- 20 volunteers tested on back
  - Visible (400-700 nm)
  - UVA1 (340-400 nm)
- BOTH induced immediate and delayed hyperpigmentation in skin type 5
- Currently available sunscreens inadequate

Mahmoud BH, et al, J Invest Dermatol 2010; 130:2092
**Sunscreens with Iron Oxide May Improve Melasma**

- Study with 20 subjects evaluated after ALA applied to arm
- Different sunscreens applied prior to visible blue light exposure
- Results: Minimal phototoxic dose (MPD) 18 hours post ALA

<table>
<thead>
<tr>
<th>Sunscreen</th>
<th>MPD (J/cm²)</th>
<th>Protection Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control- (No sunscreen)</td>
<td>0.33</td>
<td>0</td>
</tr>
<tr>
<td>A- titanium dioxide 11%, zinc oxide 2.4%, iron oxide 0.2% (Ave´ne cre´me mine´rale, SPF 50)</td>
<td>0.81</td>
<td>2</td>
</tr>
<tr>
<td>B- titanium dioxide 15%, zinc oxide 6.8%, iron oxide 3.2% (Ave´ne compact paste, SPF 50)</td>
<td>5.78</td>
<td>21</td>
</tr>
</tbody>
</table>


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**Sunscreens with Iron Oxide May Improve Melasma**

- Zinc oxide containing sunscreens
  - small particles (40 nm) provide protection mostly against UVB
  - Large particles (100 nm) provide UVB and UVA protection
  - Very large particles (> 200 nm) provide visible light protection but sunscreen appears white and is not cosmetically acceptable
- Tinted sunscreens containing iron oxide are capable of absorbing visible light
- Consider adding tinted iron-oxide (>3%) sunscreens and makeup for patients with melasma (e.g.- Avene High Protection Compact SPF 50, Femme Couture Mineral Effects Tan Pressed and Get Corrected CC Makeup)

Visible Light Sunscreen and Melasma

- 68 patients with MASI > 8
  - UV-only sunscreen with Mexoryl
  - UV + visible light sunscreen with iron oxide
- Application every 2-3 hrs X 8 wks
- All received HQ 4%
- Improvement in MASI
  - 77.8 ± 11% for visible group
  - 61.9 ± 16% for UV-only group (p < 0.001)
- Biopsies: Melanin significantly lower in visible group


Treatment of Melasma

- Sunscreens
- Cosmetics
- Discontinuation of OCP’s
- Tyrosinase inhibitors
  - Hydroquinone
  - Mequinol
  - Azelaic acid
  - Arbutin and deoxyarbutin
  - Licorice extract (liquiritin)
  - Rucinol
  - Resveratrol
  - N-acetyl glucosamine
- Stimulation of keratinocyte turnover
  - Retinoids
- Reduction in melanosome transfer
  - Retinoids
  - Soybean trypsin inhibitor
- Interaction with copper
  - Ascorbic acid
  - Kojic acid
- Kligman-Willis combination cream and variants

Sheth VM, Pandya AG, J Am Acad Dermatol 2011;65:689-714
Treatment of Melasma

- Inhibition of melanosome maturation
  - Arbutin (from bearberry)
  - Deoxyarbutin
- Inhibition of protease activated receptor 2
  - Soybean trypsin inhibitor
- Inhibition of plasmin
  - Tranexamic acid
- Glycolic acid
- Lactic acid
- Trichloracetic acid
- Pyruvic acid
- Dioic acid
- Salicylic acid
- Jessner’s solution
- Laser surgery
- Paper mulberry extract

Sheth VM, Pandya AG, J Am Acad Dermatol 2011;65:689-714

Hydroquinone vs. Placebo for Melasma

- 48 patients in Brazil treated with 12 weeks of 4% HQ or placebo bid, along with sunscreens
- 40% of HQ group, and 10% of placebo group had “total improvement”
- 57% of HQ group, and 58% of placebo group had partial improvement
- Subjective evaluation methods

**Hydroquinone**

- 5% much better than 2%
- > 15 million tubes containing HQ sold each year in the USA
- 5-10% formulas frequently compounded by dermatologists
- Penetration MAY be increased with tretinoin and glycolic acid
- Response in 4-6 weeks, maximum in 3-6 months or longer
- Irritation and ochronosis rare
- Exogenous ochronosis more common with high concentrations, lack of supervision or combination with resorcinol


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**Tretinoin, Hydroquinone, and Topical Steroids (Kligman/Willis Formula)**

- Dexamethasone 0.1%, hydroquinone 5%, tretinoin 0.1%
- Proposed mechanisms of action:
  - Tretinoin reduces atrophogenic effects of steroid, facilitates epidermal penetration of hydroquinone and reduces melanosome transfer
  - Steroid helps reduce irritation from tretinoin and decreases pigmentation on its own
  - Daily application X 5-7 weeks resulted in complete lightening
  - Results significantly less favorable if any one component was omitted
  - No cases of atrophy were seen

Kligman AM, Willis I. Arch Dermatol 1975;111:40-48
Fluocinolone acetonide 0.01%, Hydroquinone 4%, Tretinoin 0.05% (Tri-luma) Cream

- Stable, high quality variant of the Kligman/Willis Formula
- Contains class 6 corticosteroid (previously pediatric Synalar)
- Longer shelf life than compounded formulations
- Two 8-week multicenter, randomized, investigator-blind active control trials
  - Triple combination Cream compared to RA+HQ; RA+FA; HQ+FA
  - Trials encompass 13 study centers
  - 641 patients enrolled, 603 assessed


Week 8 Results: Patients with Melasma Severity Score of 0 or 1

<table>
<thead>
<tr>
<th>Study 1 (N=338)</th>
<th>Study 2 (N=303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tri-Luma</td>
<td>Tri-Luma</td>
</tr>
<tr>
<td>% of Patients</td>
<td>% of Patients</td>
</tr>
<tr>
<td>85.9%</td>
<td>67.1%</td>
</tr>
<tr>
<td>49.4%*</td>
<td>34.2%*</td>
</tr>
<tr>
<td>27.1%*</td>
<td>27.6%*</td>
</tr>
<tr>
<td>61.4%*</td>
<td>30.7%*</td>
</tr>
</tbody>
</table>

Preventing Recurrence of Melasma with TC Cream

- Randomized, investigator-blinded, controlled study
- 242 patients with melasma enrolled in 16 centers in Brazil and Mexico
- Those attaining clear or mild disease after 8 weeks of daily TC cream went into maintenance phase X 6 months
- Subjects randomized to receive TC twice weekly or a tapering regimen (3 X week for 1 month, 2 X per week for 2 months and once per week for 4 months)
- 78.8% entered maintenance phase
- After 6 months, 53% remained relapse-free
- Time to relapse was similar between groups

Arellano I, et al. JEADV 2012; 26: 611–618

Adverse Events: Combined Results

<table>
<thead>
<tr>
<th></th>
<th>TC cream N=161</th>
<th>RA&amp;HQ N=158</th>
<th>FA&amp;RA N=161</th>
<th>FA&amp;HQ N=161</th>
</tr>
</thead>
<tbody>
<tr>
<td># Pts w/ at least one AE</td>
<td>75%</td>
<td>87%</td>
<td>81%</td>
<td>59%</td>
</tr>
<tr>
<td>Application site:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>41%</td>
<td>44%</td>
<td>25%</td>
<td>16%</td>
</tr>
<tr>
<td>Desquamation</td>
<td>38%</td>
<td>61%</td>
<td>25%</td>
<td>4%</td>
</tr>
<tr>
<td>Burning</td>
<td>18%</td>
<td>23%</td>
<td>20%</td>
<td>3%</td>
</tr>
<tr>
<td>Dryness</td>
<td>14%</td>
<td>13%</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11%</td>
<td>22%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Atrophy</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Preventing Recurrence of Melasma with TC Cream

• Melasma severity at study entry, not maintenance baseline, influenced relapse rate
• The twice weekly regimen tended to show better effectiveness in postponing relapse in severe melasma
• Both regimens were safe
• QOL improved in those with improvement in melasma
• Irritation was treated by holding the TC cream for a few days and then using a moisturizing cream prior to applying the TC cream

Arellano I, et al. JEADV 2012; 26: 611–618

Atrophogenic Potential of Triple Combination Cream

• 60 patients with melasma treated with triple combination cream once daily for 12 weeks, majority Latino women
• If clear or almost clear at 12 weeks, patients entered maintenance phase, applying cream twice weekly for 12 weeks
• If relapse occurred, patients resumed daily treatment until end of study at 24 weeks
• If not clear or almost clear at 12 weeks, patients continued daily therapy for 12 weeks
• Biopsies of involved skin taken at baseline, 12 weeks and 24 weeks and compared to biopsy from uninvolved skin

Hydroquinone, Tretinoin, Steroids

- All 3 have a depigmenting effect
- A variety of formulations have been used

<table>
<thead>
<tr>
<th>HQ</th>
<th>Tretinoin</th>
<th>Topical Steroid Cream</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>0.05%</td>
<td>Betamethasone Val 0.1%</td>
</tr>
<tr>
<td>4%</td>
<td>0.05%</td>
<td>Fluocinolone acetonide 0.01%</td>
</tr>
<tr>
<td>5%</td>
<td>0.1%</td>
<td>Dexamethasone 0.1%</td>
</tr>
<tr>
<td>6%</td>
<td>0.05%</td>
<td>Triamcinolone 0.05%</td>
</tr>
<tr>
<td>2-8%</td>
<td>0.0125%- 0.1%</td>
<td>Hydrocortisone, Desonide, Mometasone, Triamcinolone, Dexamethasone, Pimecrolimus</td>
</tr>
</tbody>
</table>


Abuse of Depigmenting Creams

- Chart review of 69 Indian patients
- Unsupervised, intermittent usage was common
- High potency CS commonly used
- Side effects
  - Erythema: 43
  - Hypertrichosis: 30
  - Telangiectasias: 25
  - Acneiform eruptions: 18
  - Rosacea-like eruption: 13
  - Confetti-like depigmentation: 8
  - Epidermal atrophy: 2
  - Irritant dermatitis: 1

Kandharsi R, Khunger N, Indian J Dermatol Venereol Leprol 2013

Figure 1: Side effects due to the use of skin lightening agents; (a) Telangiectasias, (b) Acneiform eruptions, (c) Hypertrichosis, (d) Confetti-like depigmentation, (e) Rosacea-like eruption, (f) Erythema
Oral Antioxidants for Melasma

- Procyanidin made from the French Maritime pine
  - Oral use improved melasma by 20% after 8 weeks in a randomized, controlled trial of 60 women in the Philippines
- Polypodium leucotomas (Heliocare) capsules
  - Potent antioxidant made from a fern which causes increase in MED
  - One 240 mg capsule three times daily for 12 weeks vs. placebo
  - No difference compared to placebo
  - Sunscreen improved melasma by 14% (using spectrophotometer)


Tranexamic Acid

- Plasmin inhibitor and antifibrinolytic
- FDA approval in 2009 for menorrhagia
- Over the counter in some countries (UK, Sweden)
- Also used for intraoperative and trauma-related hemorrhage
- Used widely for melasma in East Asia (Japan, Korea, Singapore)
- Topical, intradermal and oral forms – latter potent and convenient

Retrospective Review of Tranexamic Acid in 561 Patients With Melasma

- Retrospective review of 561 patients in Singapore
- 91% female
- Dosed at 250 mg bid
- 91.7% improved
- Mean response in 2 months
- 7.1% with adverse effects
- 1 thrombotic event in a patient with protein S deficiency and a family history of thrombotic events who withheld history and developed a DVT
- Better results in those with older age of onset and longer duration of disease

Chee Leok Goh, MD, MRCP et al. JAAD May 2016

Randomized, Controlled Trial of Tranexamic Acid vs. Placebo for Melasma

- 44 Latino women enrolled in Dallas, Texas, 39 finished 3 months of therapy
- Randomized to tranexamic acid 250 mg bid or placebo bid
- Moderate to severe melasma, based on mMASI score
- All received sunscreen
- Primary outcome measure: mMASI
- Secondary outcome measures: Melanin index, Melasqol

Exclusion criteria

- Pregnant or nursing women
- Women on hormone therapy (birth control or replacement)
- Current treatment with blood thinning medications
- Treatment with creams, peels or laser to depigment skin within 3 months prior to enrollment
- Patients with a history of thrombosis or thrombophilia, stroke
- >2 spontaneous abortions
- Kidney dysfunction (> 1.4 creatinine)
- Cancer patients
- Smokers
- Significant cardiovascular or respiratory disease
- History of subarachnoid hemorrhage
- History of acquired disturbances of color vision
- Active thromboembolic disease such as deep vein thrombosis (DVT), pulmonary embolism and cerebral thrombosis
- Family history of thromboembolic disease


Results - mMASI

<table>
<thead>
<tr>
<th>RandomizationCat</th>
<th>Time</th>
<th>Mean</th>
<th>Std. Error</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Baseline</td>
<td>8.236</td>
<td>.360</td>
<td>7.508</td>
<td>8.965</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>6.082</td>
<td>.607</td>
<td>4.855</td>
<td>7.308</td>
</tr>
<tr>
<td>Active</td>
<td>Baseline</td>
<td>8.800</td>
<td>.360</td>
<td>8.071</td>
<td>9.529</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>3.636</td>
<td>.607</td>
<td>2.410</td>
<td>4.863</td>
</tr>
</tbody>
</table>

Placebo: mean decrease in **mMASI of 18%**
Tranexamic acid: mean decrease in **mMASI of 49%**
Side Effects

- GI upset
- Decrease in menstrual blood flow
- Headache
- Myalgias
- No serious side effects
Oral vs. Intradermal Injections of Tranexamic Acid for Melasma

- 100 Indian patients with melasma randomized to receive:
  - Oral TXA 250 mg bid
  - Intradermal injections of TXA 4 mg/ml at 10 mm intervals every 4 weeks
- 12 week duration
- MASI reduction 78% in oral group and 79% in injection group
- No serious side effects


Oral Tranexamic Acid + Triple Combination Cream

- 40 patients from Odisha, India treated for 8 weeks; not blinded
- All received cream with 2% HQ + 0.05% tretinoin + 0.01% fluocinolone once daily
- One half received tranexamic acid 250 mg twice daily
- 88% reduction in MASI in combination group vs. 55% in cream only group
- No serious side effects

Padhi T, Pradhan S, Indian J Dermatol 2015; 60:520
Topical Tranexamic Acid

- 5% TXA in liposomal gel vehicle bid not better than control in split face study of 23 women from Thailand; TXA caused erythema
- 2% TXA emulsion twice daily for 12 weeks improved 23 Korean women with mild melasma significantly; blood vessels and VEGF decreased
- 5% TXA in liposomal formulation applied to one side of face and 4% HQ to the other bid for 12 weeks in 30 women from Iran showed 52% improvement on both sides


Cysteamine 5% Cream

- Thiol compound- inhibits tyrosinase
- New technology developed to reduce its strong odor
- 55 patients from Iran applied active cream or placebo each night for 4 months
- Cysteamine cream worked better than placebo
  - MASI decreased from 17.2 to 7.2 (placebo 13 to 12)
  - Melanin index decreased from 82 to 27 (placebo 69 to 61)
- Short 15 minute application to prevent irritation
- Non prescription, $79 per tube online

Glycolic Acid Peels + Modified Kligman’s Formula for Melasma

- 40 women from India treated with serial peels + modified Kligman’s formula (MKF) vs. MKF alone for 5 months
- MKF: 2% HQ + 0.05% tretinoin cream + 1% hydrocortisone cream
- Six serial glycolic acid (GA) peels to half the patients every 3 weeks
- First 3 peels 30% GA and last 3 peels 40% GA
- Maximum time of contact was 3 minutes
- Subjective scoring methods
- Improvement in MASI

<table>
<thead>
<tr>
<th></th>
<th>Peels + MKF</th>
<th>MKF alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>45.9%</td>
<td>33.2%</td>
</tr>
<tr>
<td>21 weeks</td>
<td>80%</td>
<td>63.1%</td>
</tr>
</tbody>
</table>

- Tolerated well


Randomized, Split-Face, Investigator Blinded, Controlled Trial with Glycolic Acid Peels for Melasma

- 20 Hispanic women
- Twice daily 4% hydroquinone
- Four serial glycolic acid peels to one side of the face every 2 weeks
- First 2 peels 20% GA and last 2 peels 30% GA
- Results:
  - Both sides improved significantly
  - Both mexameter and MASI results showed NO SIGNIFICANT DIFFERENCE between both sides

Hurley ME, Pandya AG, et al., Arch Dermatol 2002; 138:1578
Randomized, Split-Face, Investigator Blinded, Controlled Trial with Salicylic Acid Peels for Melasma

- 20 patients
- Hydroquinone 4% cream to both sides of face
- Four salicylic acid peels, once every 2 weeks to one side of face
- First 2 peels - 20% SA, second two peels - 30% SA
- 8 week follow up period
- Results
  - Both sides improved
  - Both mexameter and MASI scores showed NO SIGNIFICANT DIFFERENCE between both sides

Kodali S, Pandya AG, et al, JAAD, 2010; 63:1030-1035

IPL + TC Cream for Melasma

- 56 patients from USA treated for 10 weeks
- ½ of face treated with TC cream and ½ with control cream
- Two sessions of IPL (filter 560 nm and fluence of 14-18 J to skin phototypes II–IV) at weeks 2 and 6 to the whole face
- Creams discontinued one day before to one day after IPL
- Photos at baseline, week 6 and week 10
- 57% were clear or almost clear on combination side vs. 23% on IPL only side
- Well tolerated

Low-fluence Q-switched Nd:YAG laser for melasma in Asians (Laser Toning)

- Split-face study: Q-switched Nd:YAG laser + 2% hydroquinone vs. 2% hydroquinone alone
- Parameters: 1,064-nm Q-switched Nd:YAG laser, 6-mm spot size, 3.0- to 3.8-J/cm² fluence (sub photothermolytic)
- One session every week for 5 weeks
- Results: 93% colorimeter and 76% MASI improvement on laser side compared to 20% and 24%, respectively, on control side
- 12 weeks follow up, 4/22 patients had rebound hyperpigmentation and there was at least mild recurrence of melasma in all patients despite use of 2% HQ and sunscreens
- Mottled hypopigmentation in 4 patients with darker skin (type V)

Melasma Treatment Algorithm

- Acute
  - Hydroquinone
  - Triple combination cream
  - Compounded cream
  - Tranexamic acid
  - Peels?
  - Laser?

- Maintenance
  - Arbutin
  - Kojic acid
  - Azelaic acid
  - Combination
  - 2% hydroquinone
  - Triple combination cream
    2-3 X per week

Conclusions

- There are many causes of facial hyperpigmentation
- Effective treatment first requires correct diagnosis
- Melasma is caused by increased epidermal pigmentation, which responds to many treatments, but concomitant dermal pigment is often present
- Hydroquinone remains the most effective depigmenting agent for pigmentary disorders
- Topical retinoids are effective but may cause irritation
- Topical steroids help to prevent irritation but may cause telangiectasias and thinning of skin

Conclusions

- Formulations containing hydroquinone, topical steroids, and tretinoin are useful in moderate to severe cases
- A series of peels using superficial peeling agents may shorten the time to improvement
- Newer lasers with different pulse lengths, fluences, wavelengths and treatment frequencies show some promise but hypopigmentation and rebound hyperpigmentation remain problems and more studies in a wider range of skin types are needed
- Frequent application of broad spectrum and physical sunscreens as well as avoidance of ultraviolet and visible light are important for long-term success