Update on Diagnosis, Pathogenesis and Topical Therapy for Melasma

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Acquired Disorders of Hyperpigmentation

- Post-inflamatory hyperpigmentation
- Lentigines
- Melasma
- Periorbital dark circles
- Drug-induced hyperpigmentation
- Acanthosis nigricans
- Erythema dyschromicum perstans
- Lichen planus pigmentosus
- Pigmentary demarcation lines

Melasma versus ABNOM

- Acquired Bilateral Nevus of Ota-Like Macules (Hori’s nevus)
  - More common in Eastern Asians
  - Affects 4.2% of Chinese women
  - Due to dermal melanocytes
  - Responds to laser surgery
  - Macules tend to be smaller than melasma
  - Often with blue-gray color
  - Usually on cheeks only


Melasma

- Common
- Affected by hormones
- May fade post-partum
- More common in brown races
- 90% are women
- Worsened by UV light
- Psychologically distressing
- Distinct morphology

Prevalence of Self-Diagnosed Melasma Among Premenopausal Latino Women Living in Dallas and Fort Worth, Texas

- Questions in Spanish validated in 30 women with and 30 without melasma
- 93% sensitivity and 92% specificity
- To determine prevalence, 4607 phone numbers called, with a 42.1% response rate
- 503 qualified subjects interviewed
  - 84.3% preferred Spanish
  - 95% Mexican origin
- Prevalence of melasma was 8.8%
- An additional 4% had it in past
- Risk of reporting melasma higher in Spanish speakers and in Dallas residents


Melasma is Often a Chronic Disorder

<table>
<thead>
<tr>
<th>Report</th>
<th>Ethnicity</th>
<th>n</th>
<th>Age</th>
<th>Age of onset</th>
<th>Mean duration in years</th>
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<tbody>
<tr>
<td>Guarneri et al 2003</td>
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<td>39</td>
<td>38</td>
<td>29</td>
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<td>Sanchez et al 1981</td>
<td>Latino (Puerto Rico)</td>
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<td>Kauh 1999</td>
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<td>Caucasian</td>
<td>50</td>
<td>42</td>
<td>30</td>
<td>12 (1-35)</td>
</tr>
</tbody>
</table>

Wetinger KO, et al., Arch Dermatol 2007; 143:424-425
Melasma Affects QOL

- MELASQOL is superior to the SKINDEX-16 and DLQI for melasma
- Melasma had a significant affect on:
  - Social life
  - Recreation / leisure
  - Emotional well-being
- Spanish MELASQOL showed significant affect on:
  - Social life
  - Physical health
  - Emotional well-being


UV Light and Melasma

- Distribution of lesions
- History of light exposure
- Histology of involved vs. uninvolved skin:
  - Melanogenesis
  - Melanocyte migration
  - Elastin fibers abnormal


UV Light and Melasma

- ↑ MSH is produced by keratinocytes in response to UV light
- Lesional skin compared to normal adjacent skin in 15 Korean women
  - ↑ MSH
  - No difference in ACTH
  - No difference in melanocortin-1 receptor staining
- Sustained over-expression of αMSH may be a factor in melasma

Im S, et al, Br J Dermatol 2002; 146:165

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

Sunscreen MPD (μJ/cm²) Protection Factor
- Control (No sunscreen) 0.33 0
- A- titanium dioxide 11%, iron oxide 2.4%, iron oxide 0.2% (Ave ne Cr farme, SPF 50) 0.81 2
- B- titanium dioxide 15%, zinc oxide 6.8%, iron oxide 3.2% (Ave ne compact paste, SPF 80) 5.78 21


Sunscreens with Iron Oxide May Improve Melasma

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

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- Control (No sunscreen) 0.33 0
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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

Genetic Factors and Melasma
- Incidence of melasma in family members reported by affected patients:
  - 10.2% in Singapore (Gohel D, Sing Med J 1999; 740:455)
  - 48% in a Worldwide study (Ortonne JP, JEADV 2009; 23:1254)
  - 54.7% in Iran (Moin A, Int J Dermatol 2004; 45:285)
- Melasma more common in darker skin types and certain racial groups
- Genetic studies lacking

Hormones and Melasma
- Melasma is associated with pregnancy and oral contraceptives
- Results of serum testing mixed
  - Estrogen, progesterone and MSH are increased during pregnancy
  - But circulating levels of most hormones in non-pregnant patients with melasma similar to controls in several studies
  - Estrogen levels
    - Higher in melasma group in study from India
    - Lower in melasma group in study from Puerto Rico

Exogenous Hormones and Melasma
- 212 patients attending an OB/Gyn clinic
- 29% developed melasma after oral contraceptive use
  - 87% of these patients had developed melasma during pregnancy
- Decreasing the estrogen component of the contraceptive did not alter melasma
- Oral contraceptive should be discontinued for patients who develop melasma due to this drug

Hormonal Receptor Expression in Melasma
- 33 Korean women with melasma
- Biopsy of lesional and peri-lesional skin
  - Estrogen receptor staining in dermis, particularly around vessels
  - Progesterone receptor staining in epidermis
  - Increase in hormone receptors may play a role in melasma
- Binding of estrogen to endothelial cells may be important in pathogenesis

Vasculature and Melasma
- 50 Korean women with melasma
- Biopsy of lesional and peri-lesional skin
  - Vessel size and density
  - Vascular endothelial growth factor (VEGF) expression by keratinocytes
  - Number of vessels correlated with intensity of pigmentation

Castedo-Casares, JB et al, Photodermatol Photoimmunol Photomed 2014; 30: 35–42

Castanedo-Casares, JB et al, Photodermatol Photoimmunol Photomed 2014; 30: 35–42

Resnik S, JAMA 1967;199:601


Factor Villa et al.
### Keratinocytes in Melasma Lesions Make VEGF
- Angiogenesis may be related to VEGF expression in epidermis
- An increase in colorimetry in lesional skin consistent with increased erythema
- Vascular lasers may be of benefit
- Tranexamic acid reduces vascularity and melanogenesis in melasma


### Melasma Often Has Dermal Pigmentation
- Dermal melanophages present in patients with Woods lamp-enhancing melasma:
  - 100% of 11 Latino and African American patients (Grimes 2005)
  - 35% of 43 Indian patients (Sanjay 2009)
  - 96% of 48 Mexican patients (Torres-Alvarez 2011)
  - 36% of 56 Korean women (Kang 2002)

### Increased MMP 2 and Pendulous Melanocytes in Melasma
- 5/11 Korean patients had pendulous melanocytes in lesional skin and 1/11 in non-lesional skin
- Weak type 4 collagen found below pendulous melanocytes in lesional skin compared to non-lesional skin, indicating a disrupted BMZ
- MMP 2, responsible for BMZ remodeling, was increased in lesional skin compared to non-lesional skin
- MMP2, known to be upregulated in elastotic skin, was found to be associated with elastosis in lesional skin


### Pendulous Melanocytes and Dermal Melasma
- Chronic sun exposure
  - ↓ Melanogenesis
  - ↓ MMP2 activity
- Large melanocytes
  - Weak BMZ
  - Pendulous melanocytes
  - Melanin incontinence
  - Dermal melanophages


### Fibroblasts and Melasma
- Fibroblasts (FB’s) obtained from melasma skin and buttock skin in 3 patients
- SCF and NGF higher in melasma skin
- Melasma skin FB’s as well as FB media increased melanogenesis
- Buttock skin FB’s decreased melanogenesis


### “Inflammatory” Melasma
- 197 Korean women
- Questionnaire on triggering and aggravating factors
- 50 (25%) classified as inflammatory
- Lesional and perilesional biopsies in 19 patients
- More lymphocytes, mast cells and melanophages in inflammatory group
- Anti-inflammatory agents may help patients with melasma

Photo-Contact Dermatitis and Melasma

- Much higher percentage of patients with melasma had a + photopatch test compared to controls in a Filipino study
- Fragrances, plant allergens and sunscreens were the most common offending agents
- All patients should stop potential allergens

Verallo-Rowell VM, Pua JM, Bautista D. J Drugs Dermatol 2008; 7:149-156

Principles of Melasma Therapy

- Protection from sun exposure
- Inhibition of tyrosinase activity
- Removal of melanin
- Destruction or disruption of melanin granules


Treatment of Melasma - Evidence and Experience

- Several randomized, controlled, blinded studies exist
- Several negative studies exist, which help in avoiding ineffective therapy
- Many uncontrolled, open studies
- Subjective outcome measures
- Good trials are costly
- Poor funding for melasma trials
- Combination treatments very difficult to study
- Experience is an important part of the clinical management of melasma
- More well-done studies are needed, particularly for peels and laser therapy

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

Treatment of Melasma

- Sunscreens
- Cosmetics
- Discontinuation of OCP’s
- Tyrosinase inhibitors
  - Hydroquinone
  - Mequinol
  - Azelaic acid
  - Arbutin and deoxyarbutin
  - Licorice extract (liquiritin)
  - Retinoids
  - 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-AWIs combination cream and variants

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


**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


**Adverse Events: Combined Results**
- # Pts w/ at least one AE
  | TC cream N=161 | RA&HQ N=158 | FA&RA N=161 | FA&HQ N=161 |
  | 75% | 87% | 81% | 59% |
- Application site:
  - Erythema
    | 41% | 44% | 25% | 16% |
  - Desquamation
    | 38% | 61% | 25% | 4% |
  - Burning
    | 18% | 23% | 26% | 3% |
  - Dryness
    | 14% | 13% | 14% | 3% |
  - Pruritus
    | 11% | 22% | 7% | 3% |
  - Atrophy
    | 0% | 0% | 0% | 1% |


**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)
- After 6 months, 53% remained relapse-free
- Time to relapse was similar between groups

Arellano I, et al. JEADV 2012; 26: 611-616

**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: 611-616
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>Hydroquinone (HQ)</th>
<th>Tretinoin</th>
<th>Topical Steroid Cream</th>
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<tbody>
<tr>
<td>2%</td>
<td>0.05%</td>
<td>Betamethasone Val 0.1%</td>
</tr>
<tr>
<td>6%</td>
<td>0.05%</td>
<td>Fluticasone Propionate 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: 26
  - Acneiform eruption: 18
  - Rosacea-like eruption: 13
  - Contact-like depigmentation: 8
  - Epidermal atrophy: 5
  - Irritant dermatitis: 1

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

Azelaic Acid in Melasma

- Naturally occurring dicarboxylic acid
- 20% azelaic acid equivalent to 4% hydroquinone in a 24-week double blind study of women from S. America; 65% good to excellent responses in hydroquinone group vs. 72% in hydroquinone group (Balina and Graupe, 1991)
- 20% azelaic acid found to be significantly better than 2% hydroquinone in 132 Filipino women treated for 6 mos (Verallo-Rowell et al, 1989)

Verallo-Rowell VM, et al., Acta Derm Venereol (Stockh) 1989; 143(suppl):58

Kojic Acid in Melasma

- Tyrosinase inhibitor
- 39 patients, treated with kojic acid 2% gel on one side of face and 2% hydroquinone gel on the other side bid for 3 mos.
- 5% glycolic acid in both formulations
- Clinical evaluation plus UV photos
- 51% responded equally, 28% KA better, 21% HQ better
- Mean overall decrease in pigment intensity was 58%
- Several had to change to qod frequency due to irritation


Cysteamine Cream

- Thiol compound- inhibits tyrosinase
- New technology developed to reduce its strong odor
- 55 patients from Iran applied active cream or placebo each night
- Duration 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)
- Side effects minimal

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 Philippines1
- Recently completed study in the U.S. with polypodium leucotomus (Heliocare) capsules2
  - 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)


Peeling Agents for Melasma

- Superficial peels remove stratum corneum and enhance penetration of bleaching agents
- Deeper peels may remove epidermal and dermal pigmentation
- All peeling agents may irritate and cause post-inflammatory hyperpigmentation
- Lighter skinned patients respond better to all therapies
- Postpeel hydroquinone, tretinoin, or corticosteroids are often required

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
  - Tolerated well

<table>
<thead>
<tr>
<th>Peels + MKF</th>
<th>MKF alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>45.9%</td>
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<tr>
<td>21 weeks</td>
<td>60%</td>
</tr>
</tbody>
</table>


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

70% GA Peels vs. Nanosome Vitamin C Iontophoresis

- 14 women from Egypt, skin types 4-6
- 70% GA on right side of face
- Nanosome vitamin C by iontophoresis to the left side
- Peel applied for 1-3 minutes or until patients felt burning
- 0.5 ml liposomal Vit C applied for 10 minutes using iontophoresis machine
- Total of 6 sessions, unknown frequency
- Results were modest and better with Vit C iontophoresis

Sobhi RM, Robhi MA, J Cosm Dermatol 2012

MASI scores
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

- 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
- Topical retinoids are effective but may cause irritation
- Topical steroids help to prevent irritation but may cause telangiectasias and thinning of skin
- Formulations containing hydroquinone, topical steroids, and tretinoin are useful in moderate to severe cases
- Tranexamic acid shows good efficacy in multiple studies

Conclusions

- 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