Update on Melasma

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Acquired Disorders of Hyperpigmentation

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

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 82% specificity
- To determine prevalence, 4607 phone numbers called, with a 42.1% response rate
- 500 qualified subjects interviewed
  - 96% 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 (yr)</th>
<th>Age of onset (yr)</th>
<th>Mean duration in years</th>
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<tbody>
<tr>
<td>Guerra et al 2003</td>
<td>Latino (Mexico &amp; C. America)</td>
<td>39</td>
<td>(26-52)</td>
<td>29</td>
<td>9 (3-14)</td>
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<tr>
<td>Sanchez et al 1981</td>
<td>Latino (Puerto Rico)</td>
<td>76</td>
<td>(28-68)</td>
<td>29</td>
<td>18</td>
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<tr>
<td>Kauh 1988</td>
<td>Asian (Korea)</td>
<td>45</td>
<td>(30-65)</td>
<td>31 (16-65)</td>
<td>8 (3-18)</td>
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<tr>
<td>Griffiths et al 1995</td>
<td>Caucasian</td>
<td>50</td>
<td>(30-68)</td>
<td>35 (14-56)</td>
<td>18 (1-35)</td>
</tr>
</tbody>
</table>

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

- MSH is produced by keratinocytes in response to UV light.
- Lesional skin compared to normal adjacent skin in 10 Korean women.
  - 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.
  - UV (365-400 nm).
  - UVA (320-400 nm).
  - Both induced immediate and delayed hypopigmentation in skin type 5.
- Currently available sunscreens inadequate.

Mahmoud BH, et al, J Invest Dermatol 2010; 130:2092

Sunscreen MPD (J/cm²)

<table>
<thead>
<tr>
<th>Protection Factor</th>
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<tbody>
<tr>
<td>0.33</td>
</tr>
<tr>
<td>0.81</td>
</tr>
<tr>
<td>5.78</td>
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</table>

Sunscreen 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.


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 was 11% vs. 1% for UV-only group.
  - Biopsies: Melanin significantly lower in visible group.


Vasculature and Melasma

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


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 Tin Pressed and Get Corrected CC Makeup).


Vasculature and Melasma

- 50 Korean women with melasma.
  - Biopsy of lesional and peri-lesional skin.
  - ↑ vessel size and density.
  - ↑ VEGF expression by keratinocytes.
  - Number of vessels correlated with intensity of pigmentation.

Keratinocytes in Melasma Lesions Make VEGF

- Angiogenesis may be related to VEGF expression in epidermis
- 1 a* value by 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 (Unna 2006)
  - 35% of 43 Indian patients (Bansal 2006)
  - 96% of 48 Mexican patients (Torres-Avarez 2011)
  - 36% of 58 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
- MMP2, 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


“Inflammatory” Melasma

- 197 Korean women
- Questionnaire on triggering and aggravating factors
- 80 (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
- Mustard oil (photosensitizer) use in Indian men

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

- Sunscreens
- Cosmetics
- Discontinuation of OCP’s
- Tyrosinase inhibitors
  - Hydroquinone
  - Mexoryl
  - Kojic acid
  - Estradiol
  - Licorice extract
- Retinoids
- Resveratrol
- Neocitran glucosamine

- Stimulation of keratinocyte turnover
  - Retinoids

- Reduction in melanosome transfer
  - Retinoids
  - Soybean trypsin inhibitor
  - Tranexamic acid

- 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
- Dyoic acid
- Salicylic acid
- Jessner’s solution
- Laser surgery
- Paper mulberry extract

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”
- 87% of HQ group, and 88% of placebo group had partial improvement
- Subjective evaluation methods

Hydroquinone

- 8% 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

Fluocinolone acetonide 0.01%, Hydroquinone 4%, Tretinoin 0.05% (Tri-Luma) Cream

- Stable, high quality variant of the Kligman/Willis Formula
- Contains class 5 corticosteroid (previously pediatric Synalar)
- Longer shelf life than compounded formulations.
- Two 5-week multicenter, randomized, investigator-blind active-control trials
  - Trio combination Cream compared to RA; HQ; RA+FA; HQ+FA
  - Trials encompass 13 study centers
  - 641 patients enrolled, 603 assessed

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Kligman AM, Wita J. Arch Dermatol 1975;111:45-46

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 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

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>%</th>
<th>Tretinoin</th>
<th>Topical Steroid Cream</th>
</tr>
</thead>
</table>
| 2% | 0.025% | Betamethasone 0.1%
| 4% | 0.05% | Fluocinolone 0.01%
| 8% | 0.1% | Dexamethasone 0.1%
| 2-8% | 0.1-0.5% | Triamcinolone 0.05%


Abuse of Depigmenting Creams

• Chart review of 99 Indian patients
• Unsupervised, intermittent usage was common
• High potency CS commonly used

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: 66% 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 138 Filipino women treated for 6 mos (Verballo-Rowell et al, 1989)

Verallo-Rowell VM, et al., Acta Derm Venereol (Stockh) 1989; 143(suppl):58
Verballo-Rowell VM, et al., Asian Derm Venereol (Beijing) 1989; 34:392-393
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.
- 8% 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

Farshi S, et al., Br J Dermatol 2014

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
- Recently completed study in the U.S. with polyphenol leucocomes (Helicore) capsules
  - Potent antioxidant made from a fern which causes increase in MED
  - One 240 mg capsule three times daily for 10 weeks vs. placebo
  - No difference compared to placebo
  - Sunscreen improved melasma by 14% (using spectrophotometer)

1 Farah MR, Pandya AG, et al., JAMA Dermatology 2013; 149:981-983
2 Ahmed AR, Pandya AG, et al., JAMA Dermatology 2013, 149:981-983

Tranexamic Acid
- Plasmin inhibitor and antifibrinolytic
- FDA approval in 2009 for menorrhagia
- 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
- 93.1% 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
- 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
- Tumors
- Significant cardiovascular or respiratory ailments
- History of subarachnoid hemorrhage
- Family history of thromboembolic disease


Results - mMASI

<table>
<thead>
<tr>
<th>RandomizationCat</th>
<th>Time</th>
<th>Mean</th>
<th>Std. Err</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>Baseline</td>
<td>5.299</td>
<td>.392</td>
<td>4.926</td>
<td>5.675</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>5.062</td>
<td>.224</td>
<td>4.655</td>
<td>5.469</td>
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<tr>
<td></td>
<td>6 months</td>
<td>5.060</td>
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<td>.224</td>
<td>4.655</td>
<td>5.469</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


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

Jessner Solution and TCA Peeling vs. TCA alone for Melasma

- 24 female patients from Egypt, SPT IV-V
- Split face design, 20-25% TCA
- 6 peels, 2 weeks apart
- MASI score lower on combination side
  - Jessner + TCA: 9.88 to 3.75 (64% improvement)
  - TCA alone: 10.10 to 6.56 (38% improvement)
- Tolerated well overall; more side effects on combination side

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>Peels + MKF</th>
<th>MKF alone</th>
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<tr>
<td>12 weeks</td>
<td>49.9%</td>
</tr>
<tr>
<td>21 weeks</td>
<td>80%</td>
</tr>
<tr>
<td>Tolerated well</td>
<td></td>
</tr>
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</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 to one side of face every 2 weeks.
- First 2 peels 20% SA, second two peels- 30% SA.
- 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.
- 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 hypopigmentation and there was at least mild recurrence of melasma in all patients despite use of 2% HQ and sunscreen.
- Mottled hypopigmentation in 4 patients with darker skin (types III and IV).


Triple Combination Cream + PDL for Melasma

- Dual treatment designed to target melanin and vasculature.
- 17 patients, treated with TC cream daily for 4 months.
- PDL applied every 3 weeks X 3 sessions to one side of face.
- Results:
  - Both sides improved significantly.
  - Both Mexameter and MASI results showed NO SIGNIFICANT DIFFERENCE between both sides.


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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

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