Sunscreens: Update

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I hereby certify that to the best of my knowledge, no aspect of my current personal or professional circumstances places me in the position of having private interest which is in conflict with any interest of the Academy or with my obligations to the Academy.

I have participated in advisory boards with Sanfer, Pierre Fabre, Galderma, Bioderma.
Sunscreens: Key Players
Melasma Treatment

Topical sunscreen
Photoprotection
Avoid sun exposure

Topical Depigmenting Agents
Avoid aggravant factors

Procedures

Melasma
Diagnosis
Severity
Previous treatments
Sunscreens: Key Players

Inorganic (Physical)
- MOA
- Example
- Facts

Titanium dioxide
Zinc oxide
Micronized

Photostable
- Do not react with organic sunscreens
- Might protect against visible light
- Almost no sensitisation reactions
- Undesirable: opaque, occlusiveness

Iron Oxide

Organic (Chemical)
- MOA
- Example
- Facts

Cinnamates
Salicylates
Camphors
Tinasorb N & S
Ecamsule SX & XL, etc.

Added: Antioxidants Enzymes

Reflect or scatter UV and visible radiation
- Form a film of inert metal particles.
- Form and opaque barrier.

Topical Sunscreens

Applied correctly

Enough amount
Reapplication during day
Added to other photoprotection strategies

Act absorbing UVR
- Divided in UVA, UVB and boradband
- Combination of substances is done to achieve broad protection

Are considered effective if:
- Are photochemically stable in sunlight
- If it can dissolve and disperse in vehicle
- Are non-toxic, no cause of irritation or allergy

Sunscreens: Key Players
Considerations electromagnetic spectrum

IR-A, VL & UVA
Penetrate all skin layers
reach hypodermis
Oxidative Damage

Infrared Radiation
50 – 54.3%

Visible Light
38.9 - 45 %

UVR
5 - 6.8%
0.5% UVB
6.3% UVA

Svobodová A et al Int J Radiat Biol 2010;86:999-1030
Effects of Visible Light on the Skin

• Visible light is the portion of electromagnetic radiation visible to the human eye (400-700 nm)
• Visible light exerts biologic effects in the skin.
• Can cause:
  – Erythema, pigmentation (transient and long lasting), thermal damage and free radical production.
  – Indirect DNA damage generating ROS
  – Premature photoageing

Impact of Long-wavelength UVA and Visible Light on Melanocompetent Skin

- 20 Volunteers skin type IV-VI, lower back
- The light source used emitted 98.3% visible light
- Filters added to light source to minimize IR radiation (1.5%)
- UVA1 and visible light induced pigmentation immediately
- Visible light pigmentation:
  - Dark brown, surrounded by erythema that faded in 2 hours.
  - Pigmentation was darker and more sustained
  - Remained unchanged for the study period (2 weeks)
- Skin type II: showed no pigmentation

Other important findings

• IR/visible light spectrum increased MMP-1 and MMP-9 expression and decreased type I procollagen expression; also induced macrophage infiltration. (1)

• In human epidermal equivalents exposed to visible light it was demonstrated the production of ROS, proinflammatory cytokines and matrix metalloproteinase (MMP-I). (2)

Other important findings

• VL does not induce thymine dimers formation
• Pretreatment with a photostable sunscreen with antioxidants diminished ROS production (78%) cytokines y MMP-1 (87%) in vitro
• VL induces pigmentation in vivo and ex-vivo
• VL increases tyrosinase activity and multiple exposures induce pigmentation in Caucasian skin (Conditioning)

Rhandhawa M, Seo I, Liebel F et al Plos ONE 10(6)e130949.doi:10.1371/journal.pone.0130949
Infrared radiation

- Therapeutic doses 1-10 J/cm²*
- Generates free radicals in human skin
- Depletes levels of beta-carotene and lycopene in human skin
- Angiogenesis
- Increased number of mast cells
- Decreases keratinocytes turn over
- Decreases Langerhans cell density

Importance

- Organic filters do not protect from visible light.
- Only optically opaque filters are able to absorb visible light.
- The two available inorganic sunscreen agents are zinc oxide and titanium dioxide.
- Micronized forms of metal oxides, not only scatter and reflect light, but also absorb UV.
- In 1991, Dr. Kaye et al, described that opaque physical sunscreens are useful blockers of visible light, and that transmittance of light can be lowered by adding iron oxide.

Study of efficacy of sunscreen with broad-spectrum UV protection that contains iron oxide as VL-absorbing pigment, compared with a regular UV-only broad/spectrum sunscreen, in melasma patients, exposed to intense solar conditions.
68 melasma patients were randomized in two groups. All received 4% hydroquinone and one of the two sunscreens.

**UV only:** 50+ SPF mexoryl SX & XL, titanium dioxide, octocrylene, tinosorb-S, avobenzone and ethylhexyl triazone

**UV-VL:** 60 SPF benzophenone-3, octinoxate, octocrylene, titanium dioxide, zinc oxide and iron oxide.

- MASI
- Subjective scale
- Colorimetry
- **Were performed at 2, 4, 6 and 8 weeks**

Histological evaluation at baseline and conclusion of study

Near-visible Light and UV Photoprotection in the Treatment of Melasma: a Double-blind Randomized Trial

<table>
<thead>
<tr>
<th></th>
<th>UV-Vis (29)</th>
<th>UV-only (32)</th>
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<tbody>
<tr>
<td>MASI (Reduction %)</td>
<td>77.8 ± 11</td>
<td>61.9 ± 16</td>
</tr>
<tr>
<td>Melanin fraction/mm² (Reduction %)</td>
<td>32.8 ± 14</td>
<td>19.1 ± 11</td>
</tr>
<tr>
<td>Mast cells</td>
<td>14 ± 7 to 8 ± 5</td>
<td>16 ± 12 to 12 ± 10</td>
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Prevention of Melasma Relapses with Sunscreen Combining Protection Against UV and Short Wavelength of Visible Light: A Prospective Randomized Comparative Trial

• Short wavelengths (415 nm) induce prolonged hyperpigmentation
• Long wavelengths (630 nm) do not affect pigmentation
• Study performed in real-life settings, during spring and summer
• Looking at photoprotection against melasma relapse.
• Sunscreens: same UV filter
  – Formula A: Tinted and contained iron oxides
  – Formula B: Untinted only UV
• Evaluation of MASI on standardized pictures was performed by 2 physicians masked to sunscreen used.
• Median increase of MASI score in 6 months was more important with untinted, only UV filter

40 female patients with melasma
Phototype III, IV, V

Melasma Post treatment

Formula A
Sunscreen
Color
Iron Oxide

MASI 0.45

Formula B
Sunscreen
No Color

MASI 2.45

MASI STANDARIZED PHOTOGRAPHS
2 OBSERVERS

MASI POST SPRING/SUMMER REAL LIFE SETTINGS

Other concepts to be considered
Antioxidants
Substances that offer protection to cell membranes and prevent oxidative stress to the tissues of the body by neutralizing toxic oxygen molecules and free radicals

**AO ENZYMES**
Catalyze reactions involved in the conversion of free radicals to oxygen and water

- Catalase
- Glutathione peroxidase
- Superoxide dismutase

**CHAIN BREAKING AO**
Prevent propagation of the oxidative chain reactions by terminating free radicals or the reactive products of molecules that have been damaged by free radicals

- Vit E & C
- Flavonoids
- Uric acid
- Bilirubin/albumin
- Thiol group/albumin

**PREVENTIVE AO**
Metal binding proteins that sequester free iron or copper to prevent production of the OH Radical from other free radicals

- Ferritin
- Transferrin
- Lactoferrin
- Ceruloplasmin
Photoprotection of Human Skin
Beyond Ultraviolet Radiation

• In this paper, photoprotection against IRA radiation is centered in the use of topical antioxidants.
• Only some combinations could be useful for this purpose
• One of them: Vitamin C, Vitamin E, ubiquinone and grape-seed extract, effectively prevented IRA radiation-induced MMP-I mRNA expression in vivo in human skin.
• Can be found in some sunscreens and daily care products
• Other combination described is the mixture of ferulic acid, tocopherol and vitamin C, dose dependant
• Two step strategy

Effective Photoprotection of Human Skin Against IRA by Topical Applied Antioxidants

- Randomized, controlled, double-blind prospective study
- 30 healthy volunteers
- SPF 30 sunscreen vs SPF 30 + antioxidants (Grape seed extract, Vit E & C, Ubiquinone) both groups irradiated with IRA
- Studying protection against MMP-1 upregulation induced by IRA
- Conclude that combination with topical antioxidants significantly reduced upregulation

Is there a need to add antioxidants to regular sunscreens?

IRA protection needs to be standarized for consumers

Photoprotection and Topical Antioxidants

• Never as the only product applied
• Added to sunscreen
• They have potential benefit, more in vivo research needed
• Many compounds have been studied:
  – Tocopherols and tocotrienols
  – Vitamins C & E
• Have in mind:
  – Antioxidative capacity and concentration
    • Topical 10% L-ascorbic acid 2/24hrs reduces UVB erythema*
  – Stability in formulation
  – Skin penetration

*Eberleing-Köning, Ring J Cosm Dermatol 2005;4:4-9
Systemic Photoprotection

- Never as the only photoprotective strategy
- Information supporting their use in melasma treatment

Carotenoids (β-carotene, lycopene, lutein)

Some of them

Polyphenols (flavonoids, catechins, proanthocyanidins)

Vitamin C

Polypodium leucotomos

**Polypodium leucotomos**

- Antioxidant, high content in phenolic compounds
- Oral and topical photoprotective compounds (Ferrulic, cinnamic & chlorogenic acids).
- MOA generation & release of ROS by UV and its damage to DNA, protection of natural antioxidant enzyme systems
- Decreases UV induced cellular apoptosis and necrosis
- Reduces inflammation, inhibits UV-Induced cyclooxygenase-2(COX-2) enzyme expression
- DNA damage induced by UVA and MMP1- induced by visible light and IR

**Astaxanthine**

- Xantophil carotenoid
- Cultured red algae, *Haematococcus pluvialis*
- Studies state it lowers lipids and has important antioxidant capacity
- Results suggest that effectively protects against UV-induced inflammation by decreasing iNOS and COX-2, and thereby inhibiting the apoptosis of keratinocytes.

Chou H et al Int. J. Mol. Sci. 2016, 17, 955;
β-carotene and Other Carotenoids in Protection from Sunlight

Nutritional aspect focused is complementary to topical photoprotection.

Dietary vs. supplements, dose and duration of intervention (7-10 weeks).

The concept of endogenous photoprotection requires that a protective compound is present at the site of oxidative challenge in sufficient amounts at the target site.

Some studies suggest the elevation of actinic erythema threshold.

Pigmentation was increased, lipid peroxidation diminished and the number of “sunburn cells” lower.

“The evidence available at this time is not strong enough to offer definitive support for the use of dietary carotenoids for photoprotection in healthy patients, it is sufficient to propose a role for carotenoids as adjuvant photoprotective agents”

Stahl W. Am J Clin Nutr 2012;96(suppl):1179S–84S
In summary

1. Visible Light and IRR
   - Damage the skin and are involved in photoaging, pigmentantion and coarse wrinkles production
   - Two step strategy: Iron oxide, Ti O$_2$ or ZnO

2. Advise
   - Sunscreens are mandatory in melasma treatment, sunscreens commonly used do no protect from VL & IRR
   - More research is needed Waiting for new combined products

3. Strategy
   - Antioxidants Topical & systemic

4. Available
Melasma Case

1 year in several depigmenting non HQ agents and sunscreen
Melasma Case

Week 8: Color/Iron Oxide and Retinol/HQ 4% / Week 8