Pathophysiology of melasma

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In the period of Seti I (1312-1298) the oils and ointments were very essential needs in Egypt and the ointment distribution to workers was a habit!

One day, the workers who built the temple, due to the lack of the oil to protect themselves against the sun rays, stopped going to work!

Melasma in mythology!

Melasma is a UV-induced disorder.
The term is derived from the Greek «Melas».
It means black.

Melas, the son of Poseidon, who was said to have given his name to the famous river Melas in Egypt, which was later renamed Nile!
ETHNIC DERMATOLOGY
Melasma

• 1.5-33.3 % prevalence in different populations;
  
  ➡️ Common in women, in Hispanic, Asian, African American and, Middle Eastern population
  
  (especially in darker skin phototypes!)
Classical Influencing Factors

Exposure to UV radiation
Hormonal factors
Genetic background
Cosmetics
Drugs like phenytoin
# Etiological Factors in Melasma

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<td>Sunlight</td>
<td>Typical affection of the sun exposed areas, exacerbation of the lesion by light</td>
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<td>Frequent association with oral contraceptives, pregnancy, and endocrine dysfunction</td>
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Classical causative factors have an overestimated role in melasma? 
Melasma is a component of photoaging!

The answer is NO for UV!

Lesional melasma skin show more prominent solar elastosis compared with normal skin

Melanogenesis

UVB $\rightarrow$ POMC $\rightarrow$ alpha-MSH, ACTH

Tyrosinase $\rightarrow$ Tyrosine $\rightarrow$ DOPA $\rightarrow$ C-AMP

Estrogen $\rightarrow$ MC1R

95% of the sun's UVR reaching the earth's surface is UVA!

Only 2 to 5% of UV light at the earth's surface is UVB

Practically all of UVC and much of UVB are absorbed by ozone and atmosphere! (before ozon depletion!)
Deep effect of UVA!
Role of Hormones?

- 123 patients,
  \[89.1\%\text{, deranged levels of estrogen}\]
  \[55.1\%\text{, deranged levels of PRG}\]
  \[97.1\%\text{, PRL level were normal}\]

Melasma in pregnancy

The prevalence of melasma is 50-70% in pregnancy. Hyperpigmentation in pregnancy has been attributed to increased output of some combination of placental, pituitary, and ovarian hormones; MSH, estrogen, progesterone, and bioactive sphingolipids derived from the placenta.

α-MSH level is elevated, Beta-MSH is normal in late pregnancy.
The role of ultraviolet radiation and hormonal influences

324 patients from 12 centres of nine countries;

- Half of the patients had a familial history of melasma
- Melasma affects most patients in the 3rd or the 4th decade
- The onset of the disease is found to be earlier in light skin types whereas dark skin types are usually associated with a late onset of melasma

The role of ultraviolet radiation and hormonal influences

- Only 20% of melasma occurred in the peripregnancy period
- The risk of onset during pregnancy was associated with having spent more time outdoors
- Increased use of sunscreen improved their melasma
- The contraceptive pills appear to have a weak impact
- The impact of the hormonal treatment is weak in case of familial history of melasma!

Melasma in Man?

20.5-25.83% in Indian males

Malar component is common

- Testosterone level is low (testicular resistance?)
- Nutrition - Mustard oil?
- Dietiltilbestrol therapy for prostat CA
Old causative factors have an overestimated role in melasma?

YES! There are increasing evidences showing that melanocytes are not the only cells involved, and that other players probably have a key role in the development and the relapses of melasma!

*Melasma pathogenesis and influencing factors – an overview of the latest research. T. Passeron, JEADV 2013, 27 (Suppl.1), 5-6*
Other players?

- Vascularisation
- Visible light
- Fibroblasts
- Mast cells
- Genes
- Lipid metabolism
- Keratinocytes
The vascular characteristic of melasma?

Interactions between cutaneous vasculature and melanocytes may have influence on the development of pigmentation because recent studies have suggested that:

- VGEF is known to stimulate the release of arachidonic acid (AA), and its metabolites may affect melanogenesis.
- The topical plasmin inhibitor, tranexamic acid and pulsed dye laser (PDL) are effective in the treatment of UV-induced hyperpigmentation.

Melasma & Angiogenesis

A significant increase of both the number and size of dermal blood vessels in the lesional skin is one of the major findings in melasma.

- The increase in the number of vessels is prominent than the increase in vessels size.
- The number of vessels has a relationship with pigmentation in lesional skin.

Immunohistochemistry revealed enlarged and elongated blood vessels in the upper dermis in melasma skin (B), as compared with perilesional normal skin (A).

In darker skin type, despite the use of very effective sunscreen, many patients with melasma may have relapses because:

- Both UVA and visible light are able to increase pigmentation
- The visible light pigmentation is more intense and more stable than UVA

The use of tinted mineral sunscreens is recommended because they can protect the skin both against UV and visible light!
Role of Fibroblasts?

Dermal inflammation induced by chronic accumulation of UV irradiation may be associated with activation of fibroblasts, which result in the up-regulation of C kit ligand in melasma dermal skin leading to increased melanogenesis..

Role of Mast Cells?

Mast cells were more prominent in the elastotic areas of melasma skin. Melasma could be a result of a cumulative sun exposure, in a microenvironment of cutaneous photoageing in which inflammatory cells, particularly mast cells, play a key role.

Gene Transcription in melasma

279 genes are up-regulated
Melanin biosynthesis genes
(TYR, MITF, SILV, TYRP1)

Lipid metabolism in melasma?

Lipid metabolism genes such as PPAR are down-regulated, by chronic UV exposure.

Thinning of the stratum corneum and impaired stratum corneum integrity may be a consequence of the disturbed lipid synthesis in melasma.

Role of keratinocytes?

H19, one of non-coding RNA, is down regulated in melanocyte-keratinocyte co-culture

The activation of inducible nitric oxide synthase (iNOS) and the activation of AKT/NF-kB pathway within keratinocyte induced by iNOS may stimulate melanogenesis!


Expression of iNOS and NF-κB in Melasma

An Immunohistochemical Study

Rehab Monir Samaka, M.D., Ola Ahmed Bakry, M.D., Mohamed Abd El Monaem Shoeib, M.D., and Marwa M. Zaaza, M.Sc.
Melasma pathogenesis
**Conclusion**

Melasma is a complex disorder and appears not to be only restricted to the melanocytes!

Identifying those associated factors should provide new targets for a more efficient treatment of melasma and a better prevention of the relapses!