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MELASMA ETIOLOGY AND TREATMENT: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: *Melasma is a common chronic refractory pigmentation disorder that predominantly affects women and individuals with darker skin types. It significantly alters quality of life and self-esteem because of its disfiguring skin appearance.*
Objective*: to detail current information related to melasma, etiology, epidemiology, pathophysiology, histology, presentation, treatment and prognosis.*
Methodology: *a total of 30 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 19 bibliographies were used because the other articles were not relevant to this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: melasma, laser, pigmentation, skin.*
Results: *Females are more affected than males in a 9:1 ratio. Melasma is infrequent prior to puberty and more common in the reproductive years. Melasma is found in 15% and 50% of pregnant women. The prevalence is 1.5% and 33% depending on the population. The most notable factor is exposure to sunlight. Next to pregnancy, direct sun exposure is the most important risk factor for melasma, shown by 27% to 51% of individuals as a trigger and 84% as a clinical deterioration factor. Approximately 83% to 93% of individuals with melasma have modifiable levels of solar elastosis.*
Conclusions: *The treatment of melasma continues to be a challenge, because of the fact that the spots do not disappear completely in most of those affected, in addition to presenting considerable recurrence rates. The first line management is adequate sun protection and the association of sunscreens with color and topical bleaching agents, which may have a different effect on melanogenesis. In case oral medications are needed, tranexamic acid presents the best evidence for treatment. Some procedures support the treatment of melasma, such as microneedling and chemical peels that act through epidermal renewal. Lasers should be used with extreme caution because heat induces post-inflammatory melanogenesis. The combination of topical bleaching agents with medications and oral procedures provides more rapid effects, however more studies are needed regarding the treatment of the condition.*

KEY WORDS: *melasma, laser, pigmentation, skin.*

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INTRODUCTION

Melasma is a common chronic refractory pigmentation disorder that predominantly affects women and individuals with darker skin types. It significantly alters quality of life and self-esteem because of its disfiguring appearance on the skin. The overall prevalence ranges from 8.8% to 40%, depending on the ethnicity of the population and location. It usually appears on the cheeks, chin, bridge of the nose, forehead and above the upper lip. There are currently several treatments available for melasma, with mixed results, because the therapeutic management of this pathology is considered a challenge due to the high recurrence rates that greatly alter the quality of life of affected individuals. Pregnancy is a common cause of melasma, just as melasma occurs in women taking oral contraceptives and hormones. At the time of the study no single treatment is completely effective. There are studies showing promising results with systemic treatments with tranexamic acid and Polypodium leucotmatous, however, the former was associated with several systemic side effects. Microneedling and peeling are also alternatives considered effective in some studies, although their superiority over topical hydroquinone, which is the gold standard in the management of melasma, has not been established at this time. Likewise, laser and light devices have been useful. Combination therapies have better results than single therapies. It is recommended that the choice of treatment be made appropriately after Wood's lamp examination and dermoscopic evaluation to choose the best treatment alternative for each subtype of melasma(1-7).

METHODOLOGY

A total of 30 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 19 bibliographies were used because the information collected was not important enough to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: melasma, laser, pigmentation, skin.

The choice of literature exposes elements related to melasma, etiology, epidemiology, pathophysiology, histology, presentation, treatment and prognosis.

DEVELOPMENT

Melasma is a common recurrent pigmentary disorder that significantly alters quality of life and at present there is no curative treatment available. Photoprotection against UVB, UVA and blue-violet visible light is critical to treatment victory, as are topical therapies that lead to tyrosinase inhibition; hydroquinone and triple combination cream are the gold standard drugs. Oral therapies with tranexamic acid and microneedling along with topical therapies can significantly increase the efficacy of management. Superficial peels and low-fluence laser therapy increase melanin clearance from the epidermis, which accelerates clinical results(8).

Etiology

The etiological factors of the condition are several such as ultraviolet (UV) radiation, pregnancy, genetics, hormonal therapies, phototoxic drugs, anticonvulsant drugs and some cosmetics. Melasma stimulates melanocytes through female sex hormones estrogen and progesterone, producing more melanin pigments when the skin is exposed to the sun(9-11).

Melasma is more common in the female sex, with genetic predisposition being a notable factor in the development of melasma. Individuals with light brown skin in parts of the world with high sun exposure are more likely to have the condition. About half have a positive family history of the condition, and identical twins with melasma have been reported.Ultraviolet radiation can generate peroxidation of lipids in cell membranes, originating free radicals that stimulate melanocytes to produce excess melanin. The longer wavelengths of UV-A and visible radiation (320-700 nm) are not blocked by sunscreens that block UV-B radiation (290-320 nm), thus stimulating melanocytes to produce melanin. Hormones may play a role in the development of melasma in certain individuals; there is evidence of a 4-fold increase in thyroid disease in individuals with melasma; in addition, there is a relationship between the development of melasma and having melanocytic nevi or lentiginous nevi, which would show a relationship between the development of melasma and the presence of pigmentation.

Mask-like appearance in pregnancy is relatively common, the mechanism is not yet fully elucidated, however it is thought that estrogen, progesterone and melanocyte stimulating hormone levels normally increase during the third trimester of pregnancy, becoming an important factor in its development. Women with nulliparous melasma do not have increased levels of estrogen or MSH, however, they have elevated amounts of estrogen receptors within the lesions. On the other hand, melasma has been seen with oral contraceptive pills containing estrogen and progesterone, as well as diethylstilbestrol treatment for prostate cancer. A postmenopausal patient given progesterone may form melasma, whereas those given estrogen alone do not, suggesting that progesterone plays a crucial role in the formation of melasma.

Epidemiology

It usually affects people of any race. Melasma is more common in darker skin types compared to lighter skin types, and is uniquely more common in light brown skin types. Women are more affected than men by a 9:1 ratio. Melasma is uncommon prior to puberty and more common in the reproductive years. Melasma is found in 15% to 50% of pregnant women. The prevalence is 1.5% and 33% depending on the population.

Pathophysiology

The most notable factor is exposure to sunlight. Ultraviolet radiation induces the manufacture of alpha-melanocyte stimulating hormone and corticotropin, as well as endothelin 1 and interleukin 1, helping to increase melanin generation by

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intraepidermal melanocytes. Dermal inflammation induced by constant UV exposure and fibroblast activation positively regulates stem cell factors in the dermis of melasma, resulting in increased melanogenesis. Next to pregnancy, direct sun exposure is the most important risk factor for melasma, shown by 27% to 51% of individuals as a trigger and 84% as a factor of clinical deterioration(3,8,12,13).

Histopathology

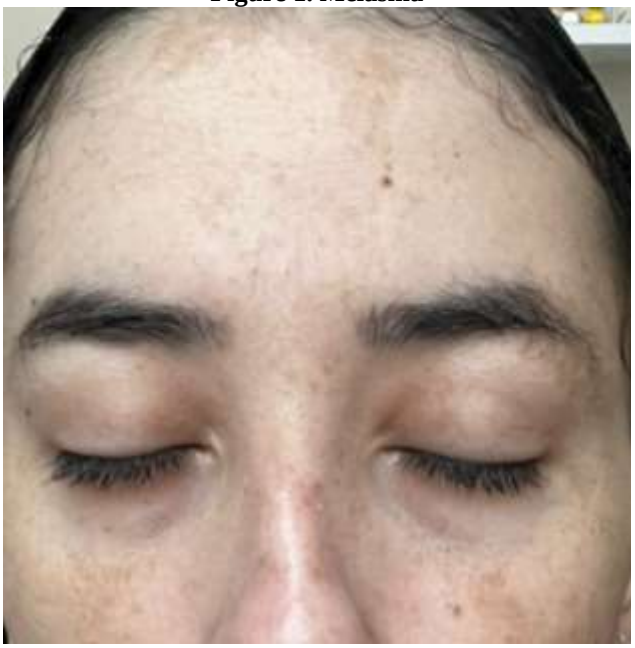
Melanin increases in the dermis, epidermis or both. Epidermal melanin is located in keratinocytes in basal and suprabasal locations. Dermal melanin may also be in the superficial and mid dermis within macrophages that cluster near small, dilated vessels. Inflammation is almost absent and sometimes absent. Approximately 83% to 93% of individuals with melasma have modifiable levels of solar elastosis(3,14-16).

Evaluation

Melasma usually appears on sun-exposed surfaces as an acquired hypermelanosis, resembling symmetrically distributed hyperpigmented macules that may appear both confluent and punctiform. They occur mostly on the cheeks, upper lip, chin and forehead.

Laboratory tests are not indicated, although there are studies suggesting association with mild abnormalities in thyroid function, especially when it refers to melasma associated with pregnancy or the use of oral contraceptive pill, where it is possible to consider the use of thyroid function tests. Wood's lamp examination allows locating the pigment in the dermis or epidermis(14,17).

Figure 1. Melasma



Source: The Authors.

Treatment

Treatment of melasma is a major challenge, especially since it is prone to constant relapses despite proper removal. Some literature shows that the best treatment is a topical combination of hydroquinone cream and avoidance of sun or estrogen exposure. The use of sunscreens has an important role in prevention. The first line treatment for melasma consists of effective topical therapies, especially in the form of triple combinations (hydroquinone 4%, tretinoin 0.05% and fluocinolone acetonide 0.01%), although dual treatments can also be used(3,18).

Chemical peels and lasers can generate unpredictable effects and are associated with adverse effects such as post-inflammatory hyperpigmentation, epidermal necrosis and hypertrophic scarring. These interventions are used as a second line, although it is recommended to use them only in case of previous therapeutic failure; correctly applied chemical peels and lasers usually generate fast results compared to topical medications. Skin peels have a risk of adverse results, the peels use elements based on glycolic acid and salicylic acid that increase the renewal of hyperpigmented keratinocytes. They usually start monthly with low concentration formulas and are followed by weekly applications at higher concentrations. Lightening agents are used in combination with superficial peels to show better effects. Skin peels should only be used after a test therapy with at least one skin lightening agent. Extensive monitoring of skin depigmentation is required and treatment should be discontinued if necessary.

The efficacy of laser for the treatment of melasma is associated with undesirable cosmetic effects. In cases of extensive disease that is refractory to the use of laser, it may worsen the condition(3).

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Platelet-rich plasma (PRP) may be another promising form of treatment for melasma, but there is currently no consensus on a standardized method of PRP preparation or platelet concentration. Platelets present several elements such as epidermal growth factor, platelet growth factor, transforming growth factor (TGF) β1 and β2. Which exert on pigment metabolism and inflammation and reach to restore dermal structures affected by melasma(8).

Research evidence that radiofrequency microneedling is an effective treatment for refractory melasma, however, more studies on the subject are needed(19).

Other studies also reported that hydroquinone monotherapy and triple combination cream are the most effective treatments and improving melasma, leaving chemical peels and laser and light based therapies as equal or inferior to topicals,generating more risk of adverse effects. Oral tranexamic acid can be used as a systemic adjunctive treatment, but more evidence is needed to demonstrate its long-term safety and efficacy(2).

Figure 2. Melasma before and after treatment.

Source: Cassiano DP, Espósito ACC, da Silva CN, Lima PB, Dias JAF, Hassun K, et al. Update on Melasma-Part II: Treatment(8).

Differential Diagnosis

- Frictional melanosis.
- Mastocytosis.
- Nevi of ito and Ota.
- Actinic lichen planus.
- Drug-induced photosensitivity.
- Exogenous ochronosis.
- Poikiloderma of Civatte.
- Postinflammatory hyperpigmentation.
- Acanthosis nigricans.
- Discoid lupus erythematosus.
- Pigmented contact dermatitis.

Prognosis

According to several studies, melasma has no associated morbidity or mortality because no cases of malignant transformation or association with increased risk of melanoma or other malignant neoplasms have been reported; on the other hand, individuals affected with melasma are considered to have a lower risk of developing melanoma. Dermal pigment may take slightly longer to clear compared to epidermal pigment because there is no effective therapy to remove dermal pigment. However, management should not be terminated by a preponderance of dermal pigment alone. The origin of dermal pigment is the epidermis and by having an inhibited epidermal melanogenesis for long periods, the dermal pigment will not be replenished and will gradually resolve. Resistance or recurrences of melasma happen relatively frequently and will occur more easily if sunlight is not strictly avoided(3).

CONCLUSIONS

The treatment of melasma continues to be a challenge, because the spots do not disappear completely in most of those affected, in addition to presenting considerable recurrence rates. The first-line management is adequate sun protection and the association of sunscreens with color and topical bleaching agents, which may have a different action on melanogenesis. In case oral medications are needed, tranexamic acid presents the best evidence for

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Conflict of Interest Statement

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