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REVIEW ARTICLE

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Melasma: How hormones can modulate skin pigmentation

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Summary

We described—along with a genetic predisposition and exposure to sunlight, as the main factors for melasma development—pregnancy, hormonal therapies, and oral contraceptive pills. Whilst hormonal alteration or therapies are frequently reported in literature in association with melasma, studies analyzing the laboratoristic correlation are limited. We review data published on hormones variations both in women and males with melasma and report some peculiar clinical cases that further demonstrate how the relationship between hormone secretion and melasma development is difficult to be defined.

KEYWORDS

hormones, melasma, pigmentation

1 | INTRODUCTION

Melasma is a relatively common acquired disease, characterized by a pattern of emarginated, symmetric, light-to-dark brown facial hyperpigmentation. Some areas of the skin are more exposed to the sun, such as the cheeks, forehead, upper lip, nose, and chin and sometimes, neck as well.

According to their distribution, melasma is classified into three types: centrofacial, malar, and mandibular patterns.[1] Histologically, melasma is characterized by excessive melanin deposition in the epidermis (epidermal type, 70%), dermal macrophages (dermal type, 10%), or both (mixed type, 20%). Melasma considerably affects patients' quality of life—with considerable emphasis on its therapeutic difficulty. Melasma is usually clinically diagnosed; however, Wood's lamp examination, confocal microscopy, and histology are helpful tools for distinguishing epidermal from dermal melasma.[2]

Women of Hispanic and Asian origin are more commonly affected by melasma.[3] Melasma affects most patients in the 3rd or the 4th decade of life; 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.[4]

Although the prevalence of melasma among various ethnic groups and skin phototypes is different, the preferential development of melasma during women's reproductive age and the association of this disease with oral contraceptives suggest that female sex hormones accelerate the development and aggravation of melasma—even if the impact of female hormones has been recently minimized.[4] During pregnancy, in particular in the third trimester, the levels of placental, ovarian, and pituitary hormones, which are a stimulus for melanogenesis, are increased. According to different observations,[5] melasma in pregnancy is more likely to be associated with circulating female hormones than melanocyte-stimulating hormone (MSH) peptides. Through the induction of synthesis of melanogenic enzymes such as tyrosinase and tyrosinase-related proteins 1 and 2, estrogens stimulate melanogenesis in cultured human melanocytes. The increase in progesterone levels that occurs during pregnancy and the increase in estrogen production that occurs from the eighth to the thirtieth week of pregnancy reflects, indeed, the typical pattern of progression of hyperpigmentation. Epidemiological data showed that melasma occurs in 14.5%-56% of pregnant women and in 11.3%-46% of individuals who take oral contraceptives in different countries.[6] A study performed on 324 women with melasma in nine different countries worldwide revealed that melasma occurs in only 20% of cases in pregnancy and almost 10% start after menopause. In addition, the study demonstrated that cessation of contraceptive pills weakly affects the development of the disease.[7] Melasma has been considered as a consequence of contraceptives with synthetic progestin levonorgestrel,[8] even if the role of progesterone in skin pigmentation has to be established. It has been found out that progesterone is involved in the pathogenesis of melasma by stimulating melanogenesis in the epidermal melanocytes.[9] Conversely, others suggested the prevention of melasma by progesterone components

in oral contraceptives since progesterone can reduce melanocyte proliferation without significant effects on tyrosinase activity.[10]

Considering that female sex hormones in oral contraceptive pills are factors involved in the development of melasma, we could anticipate a similar relationship in postmenopausal women taking hormone replacement therapy. Melasma of the forearms has been described in postmenopausal women taking hormone replacement therapy.[11] Although a case-control study[12] in 45 patients with extra facial melasma found no differences with the control group in hormone treatment, hormone replacement therapy or current or prior oral contraceptive use. There are various reports of cases of systemic hormones as trigger for the development of melasma. In addition, the development of melasma after application of topical estrogen cream has been observed.[13]

The activities of estrogens and progesterone are mediated by particular receptors of human skin, among which the estrogen receptors (ERs) ER-alpha/ER-beta and progesterone receptors (PRs)—respectively.[14] In vivo studies provide conflicting data on different expression of ER and PR receptors in melasma lesional skin.[15,16] The expression of ERs varies depending on the location and tissue type; moreover, it has been shown that skin on the face expresses much higher concentrations of ERs than the breast or the thigh.[17] ER-beta is more widely distributed within the skin and skin structures than ER-alpha. The variation in distribution of receptors within the skin suggests that each of them plays a different, cell-specific role,[18] which, to date, has not been clarified.

Whilst the role of hormones in melasma pathogenesis is frequently reported in literature from an epidemiological point of view, studies analyzing the laboratoristic correlation are limited. Our aim is to review the literature on blood levels of hormones in women and men with melasma and to report how a clear correlation is difficult to be identified.

2 | HORMONAL LEVELS IN WOMEN WITH MELASMA

Perez et al[19] analyzing the hormonal levels in nine patients with melasma reported mild ovarian dysfunction with elevated LH, low mean follicular 17-β-estradiol, and normal plasma levels of α-MSH, FSH, progesterone, and prolactin; an ER sensitivity in both the hypothalamopituitary axis and the melanocytes has been suggest as roles in the induction of melasma.

Differences in the levels of LH, FSH, and 17-β-estradiol at the beginning of the menstrual cycle among the groups have been found in an Indian study that compares FSH, LH, prolactin, estrogen, and progesterone among 36 women with melasma and controls of the same age. This suggests that circulating estrogens may constitute a risk factor and maintainer of the disease. Serum prolactin was lower on day 9 in the study group than in the control group; there was no difference in progesterone levels in patients with melasma on day 17, 19, and 21, comparing with the control group. Another study in 138 Pakistan women reported a significant increase in estradiol levels both in the follicular and luteal phases in patients with melasma, when compared to the controls.[20]

Analyzing 30 female patients with melasma and 30 age-matched controls, Gopichandani et al[21] found statistically significant lower estradiol, progesterone, free testosterone, and total testosterone in melasma cases. Gopichandani discovered a significant decrease in LH in melasma patients, suggesting mild pituitary dysfunction. The decreased estradiol levels in melasma patients are in agreement with findings of Pérez et al and corroborate the hypothesis that mild ovarian dysfunction might be a causative factor in the development of melasma.

We have found no other comparative studies regarding total or free testosterone levels in the literature in women with melasma.

Adalatkhah[22] reported significant decrease in mean serum levels of Dehydroepiandrosterone sulfate (DHEAS) without difference in the levels of prolactine, testosterone, 17 hydroxyprogesterone, FSH, and LH in 101 subjects with melasma. Moreover, a significantly increased presence of ovarian cysts in melasma patients was observed respect than controls, confirming the possible role of ovarian cysts, and androgenic hormone in melasma.[23]

3 | HORMONAL LEVELS IN MEN WITH MELASMA

Epidemiological studies showed that melasma in men is not so uncommon as believed,[24] but endocrinological aspects are infrequently evaluated. The first case of melasma in a male patient was reported in 1957 in a French man with primary hypogonadism, reduced testosterone, and increased levels of LH and FSH.[25] Similarly, Sarkar[26] and Sialy[27] reported reduced levels of testosterone and increased levels of LH in men with melasma compared to age-related controls, suggesting a subtle level of testicular resistance.

Burkhart et al[28] reported a case of melasma after oral therapy with gonadotropic stimulator that leads to the increase of LH secretion and testosterone production, containing dehydroepiandrosterone (DHEA), androstenedione, indole-3-carbinol, and *Tribulus terrestris*. On the contrary, an increase in the number of male patients with melasma has been reported after the arrival of finasteride, an antiandrogen. [29] O'Brien reported a possible pathogenetic role of estrogens, describing a case of melasma of the forearms in a man who had been treated with exogenous estrogens for prostatic carcinoma.[30]

A study on 41 men with melasma reported hormonal alteration only in 9.7% of patients suggesting as the main causative factors of melasma, sun exposure, and family history. Similarly, Handa[31] did not observe any significant difference in circulating hormone levels between 50 men with melasma and healthy controls. Therefore, the role of hormones in the onset of melasma in men is contrasting and need to be verified in studies with larger sample sizes.

4 | CASE SERIES

We report some peculiar clinical cases that further demonstrate how difficult it is to demonstrate a clear relationship between hormone role and melasma development.

4.1 | Case 1

A 36-year-old Caucasian man with Fitzpatrick skin type III presented to our clinical observation with the presence of symmetric hyperpigmented macules of melasma with a malar pattern, localized on the periorbital, cheeks, and temporal regions (Figure 1). The macules were irregular ranging in color from beige to brown. Wood's lamp examination evidenced a dermo-epidermal distribution of hyperpigmentation. Family history was negative for melasma. The patient was an athlete and had consumed a testosterone enanthate 250 mg dose twice per week for 10 weeks followed after 4 months by methyltestosterone dose of 10 mg dose three times per week for 10 weeks. He had been taking such drugs cycles since 4 years. Melasma lesions appeared 2 years after the starting of hormones assumption. He denied the use of any topical chemicals or cosmetics before the appearance of melasma. No signs of hyperandrogenism and/or other kinds of side effects were detectable. The patient was not married and did not have children.

4.2 | Case 2

Our second patient was a 35-year-old caucasian female-to-male transgender with Fitzpatrick skin type III referred to our outpatients department for the appearance of hyperpigmented macules and patches ranging in color from beige to brown, distributed symmetrically on centrofacial areas. Wood's lamp examination and UV digital image analysis (Visoface® RD; Courage + Khazaka electronic GmbH) confirmed the diagnosis of dermo-epidermal melasma. Melasma manifestations aroused few months after starting the ongoing masculinizing hormone therapy based on testosterone enanthate (intramuscular 100-200 mg every 2 weeks). The patient had no previous history of similar skin lesions and denied any possible triggering factors of melasma such as sunlight exposure, thyroid disease, cosmetics, and family history of melasma. The patient used to wear sun hat and daily sunscreens (SPF 50+) and did not use to go to the sun.

4.3 | Case 3

We report a case of a 35-year-old Caucasian woman with a 2-year history of asymptomatic brownish macules on the face. The irregular hyperpigmented lesions were localized on cheeks, upper lips, and forehead, and the diagnosis was consistent with melasma (Figures 2,3).

In April 2017, she had undergone breast surgery for an infiltrative ductal carcinoma and, in October 2017, she was started on tamoxifen. After about a 3-month administration of tamoxifen,

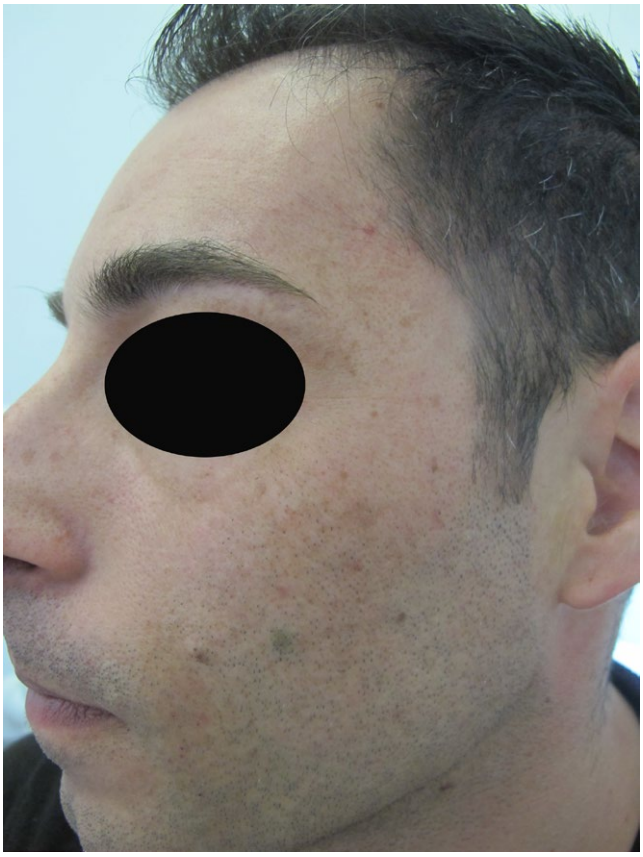

FIGURE 1 A 36-y-old Caucasian man with Fitzpatrick skin type III with symmetric hyperpigmented macules of melasma on the periorbital, cheeks, and temporal regions

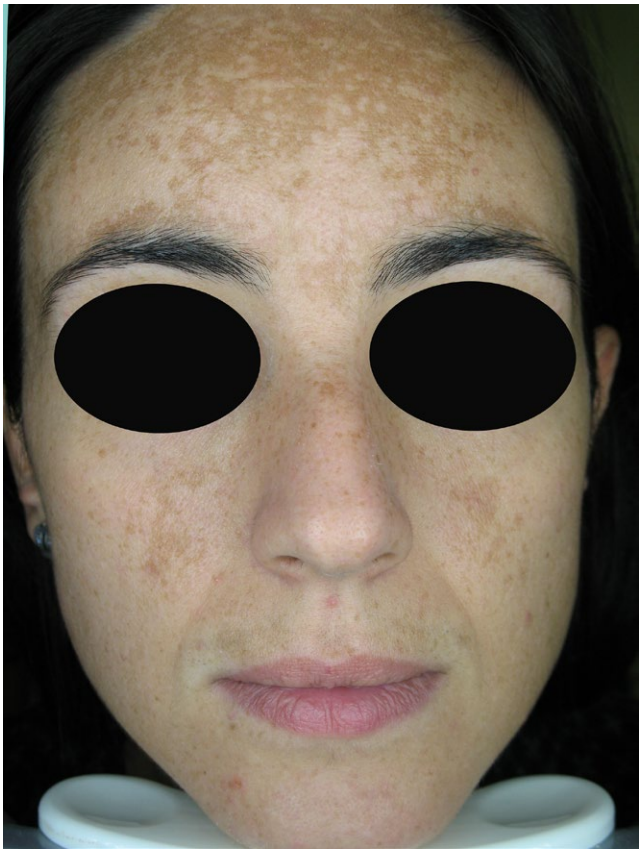

FIGURE 2 Digital photograph of a 35-y-old Caucasian woman with a 2-y history of melasma during tamoxifen therapy for breast cancer

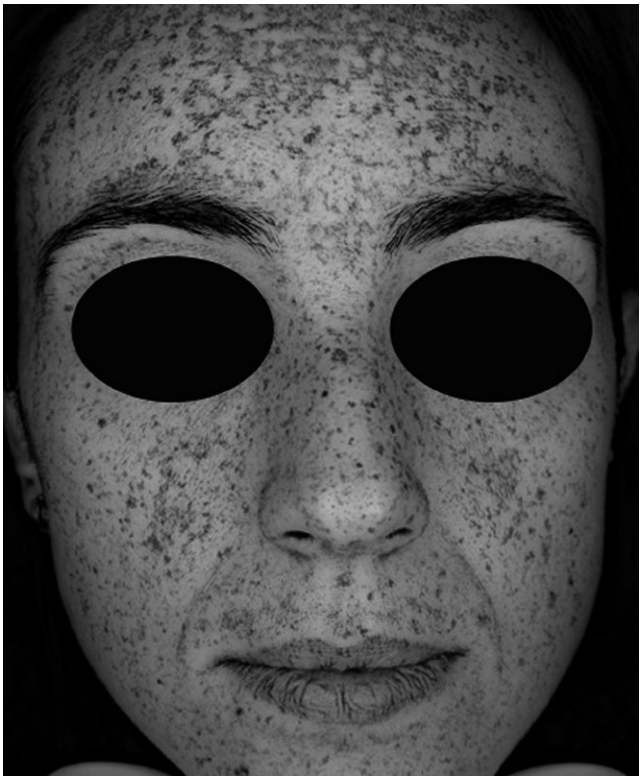

FIGURE 3 UV image analysis of a 35-y-old Caucasian woman with a 2-y history of melasma during tamoxifen therapy for breast cancer

symmetric brownish, hyperpigmented macules with irregular borders and diameter occurred on the face. At clinical examination, the patient did not show hypertrichosis or hair loss signs. The diagnosis of melasma (dermo-epidermal) was confirmed by digital image analysis and Wood's lamp observation. She had no previous history of similar skin lesions, and she denied any possible triggering factors of melasma such as sunlight exposure, thyroid disease, cosmetics, and family history of melasma.

4.4 | Case 4

A 39-years-old Caucasian man, Fitzpatrick type III, came to our observation for the presence of brown symmetric patches distributed on the cheeks (Figure 4). The patient was affected by androgenic alopecia, treated in the past with topical minoxidil (5%) without any clinical improvement. Topical minoxidil application was than interrupted and systemic therapy with finasteride (1 mg daily) was started 3 years ago. The hyperpigmented lesions of the face aroused 2 years after the starting of finasteride systemic treatment for androgenic alopecia. The clinical and instrumental (Wood's lamp examination and Visioface® UV digital image analysis) diagnosis was melasma with a prevalent dermo-epidermal pattern.

No causative factors or anamnestic familial history were reported, and the patient denied sunlight exposition.

Even after having carried out the blood dosages, the treatment with testosterone in the male patient who assumed it for an agonistic reasons was superior to that used for the treatment of male hypogonadism, then presumably reaching higher plasma concentrations than normal ones of an adult man.

Also, in the female-to-male transgender the testosterone intramuscular injections and its overdosage induced amenorrhea.

In the woman assuming tamoxifen, an antiestrogen, the patient was undergoing oncological therapy which therefore included a complete block of the receptor activity.

Regarding the patient who had taken the finasteride, the latter does not modify the hormonal levels, but modifies the receptor response to the hormonal stimulus, so there was no need for blood dosage.

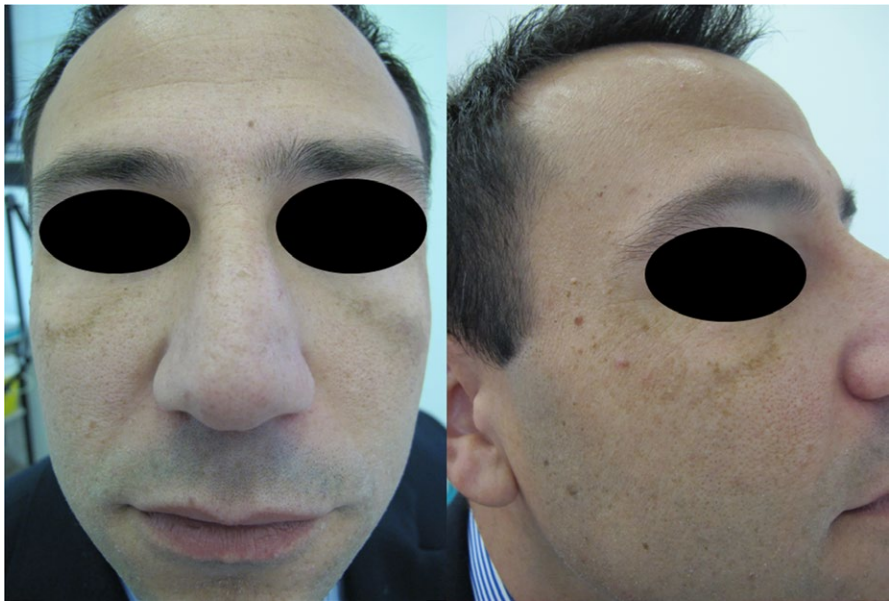

FIGURE 4 A 39-y-old Caucasian man, Fitzpatrick type III, with brown symmetric patches of melasma distributed on the cheeks

5 | CONCLUSIONS

Although some triggering factors, such as sun exposure, pregnancy, use of oral contraceptives, ovarian tumors, hepatopathies, hormone replacement therapy, inflammatory processes of the skin, use of cosmetics, and photosensitizing drugs[32,33] are described, the exact causes of melasma remain unknown. Our literature review shows that the correlation between melasma onset and hormonal changes in both men and women is not clear.

Also, the description of our particular cases shows that despite the assumption of different and antagonistic hormonal therapies (anti-estrogen and anti-androgens) melasma can appear.

These clinical evidences and the new data regarding melasma correlation with photoaging support how different factors can play a major role in the pathogenesis of melasma.

Other factors, which could alter sex hormone metabolism, including interindividual alteration in synthetic enzymes may contribute to cause the conflicting outcome. Other cellular and paracrine regulatory factors, such as receptor expression and functionality, are involved in estrogen responses.[4] Moreover, according to recent data analysis, genetic influences and exposure to UV radiation probably cause melasma pathogenesis. In fact, the increase of elastotic materials in skin biopsy specimens indicates that the accumulation of sun exposure is necessary for the development of melasma.[34]

Paracrine associations between keratinocytes, fibroblasts, and melanocytes in the skin probably play an important role in regulating epidermal melanization.[35] In response to UV, human keratinocytes and fibroblasts secrete one of the melanogenic cytokines, SCF, that acting on c-Kit receptors on melanocytes, cause hyperpigmentation.

In addition, melasma predilection for the centrofacial region, where the sebaceous gland density is the highest, suggest a possible association between sebaceous function and melasma pathogenesis. Sebaceous glands, synthesizing several cytokines, and growth factors, such as angiopoietin and adipokine, can modulate melanocyte function. Moreover, sebocytes are under the control of αMSH, and therefore, an overexpression of this hormone can influence both types of cells. Overall, these data suggest that melasma is a manifestation not limited only to the melanocytes, but involving different skin cells subpopulations. Considering that pigmentation is strictly dependent on the cross talk among the different skin cells, other cells can be taken in consideration as therapeutic target in melasma treatment.

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CONFLICT OF INTEREST

None.

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