THE ROLE OF ENDOCRINE IN MELASMA: WHAT'S NEW?

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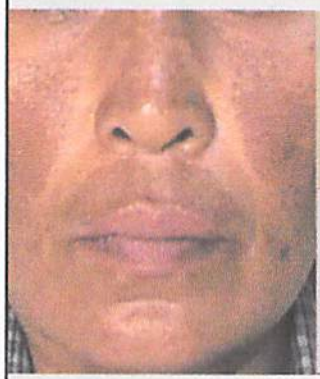
Outline

1. MELASMA AND FEMALE SEX HORMONE
2. MELASMA AND THE PITUARY GLAND
3. MELASMA AND THYROID HORMONES

Introduction



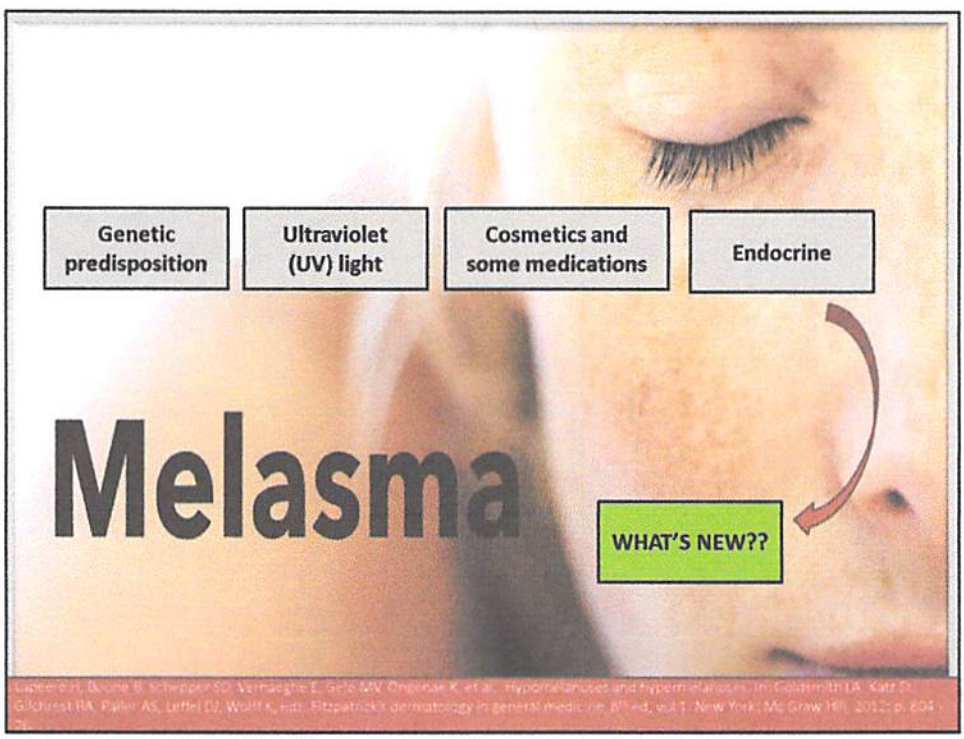
MELASMA

An acquired disorder of melanogenesis leading to hyperpigmentation and manifested by almost always symmetrical brown to gray-black macules and patches with serrated irregular edges.

It occurs especially in sun-exposed areas.

Melasma occurs in all ethnic groups. It is particularly common in individuals of darker pigmented skin phenotypes (such as Fitzpatrick skin types III to IV). It is more common in women than men; the prevalence ranges from 1% to 35%

Lapeere H, Boone B, Schepper SD, Vermaeghe E, Grine MV, Ongenae K, et al. Hypomelanoses and Hypermelanoses. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, eds. Fitzpatrick's dermatology in general medicine. 8th ed, vol 1. New York: Mc Graw Hill. 2012. p. 804-16.



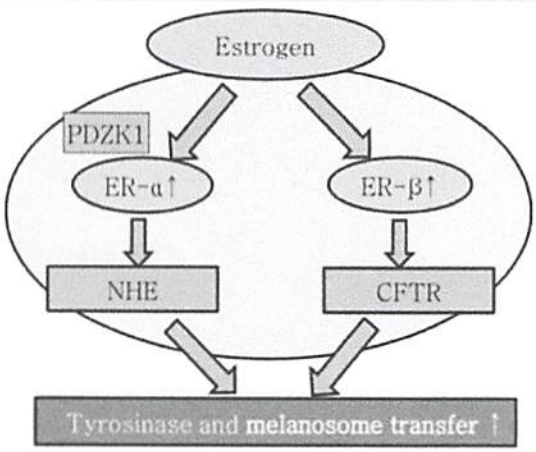
Lapeere H, Boone B, Schepper SD, Vermaeghe E, Grine MV, Ongenae K, et al. Hypomelanoses and Hypermelanoses. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, eds. Fitzpatrick's dermatology in general medicine. 8th ed, vol 1. New York: Mc Graw Hill. 2012. p. 804-16.

MELASMA AND FEMALE SEX HORMONE

- Melasma occurs because the stimulation of melanocytes by female sex hormones estrogen and progesterone can produce more melanin pigment when the skin is exposed to sunlight.
- Many cases are associated with excessive estrogen levels, either endogenously produced during pregnancy or given exogenously through oral contraceptive use and hormone replacement therapy

Muller I, Rees A. Melasma and endocrine disorders. Journal of Pigmentary Disorders. 2014;1:5.

Schematic view of the role of estrogen-induced hyperpigmentation in melasma.



Increased ER expression indicates a potential role of estrogen in melasma
Cultured normal human keratinocytes and melanocytes express PDZK1, **PDZK1 could facilitate the estrogen action** by interaction with other proteins including ion exchangers, resulting in the stimulation of **melanogenesis and melanosome transfer** in melasma

Lee AY. An updated review of melasma pathogenesis. Dermatol Sin. 2014;32:233-9.

J Invest Dermatol. 2012 Nov;132(11):2622-31. doi: 10.1038/jid.2012.175. Epub 2012 Jun 14.

PDZK1 upregulation in estrogen-related hyperpigmentation in melasma.

Kim NH[1], Cheong KA, Lee TR, Lee AY

⊕ Author information

Abstract

The pathogenesis of melasma is unknown, although the potential role of estrogen has been considered. Microarray and real-time PCR analyses revealed that upregulation of PDZ domain protein kidney 1 (PDZK1) is clinically correlated with melasma. Although there has been no report that PDZK1 is involved in pigmentation and/or melanogenesis, PDZK1 expression can be induced by estrogen. In this study, the role of PDZK1 upregulation in melasma was examined, particularly in connection with estrogen, using biopsied skin specimens from 15 patients and monocultures and cocultures of melanocytes and keratinocytes with or without overexpression or knockdown of PDZK1. Estrogen upregulated PDZK1. Overexpression of PDZK1 increased tyrosinase expression and melanosome transfer to keratinocytes, whereas PDZK1 knockdown reduced estrogen-induced tyrosinase expression, through regulation of expression of estrogen receptors (ERs) ER-α and ER-β. The PDZK1-induced tyrosinase expression and melanosome transfer was regulated by ion transporters such as sodium-hydrogen exchanger (NHE), cystic fibrosis transmembrane conductance regulator (CFTR), and SLC26A3, which showed a specific association with each ER subtype. In the melanosome transfer, PDZK1 also increased phosphorylation of ezrin/radixin/moesin (ERM) and ras-related C3 botulinum toxin substrate 1, but not the expression of proteinase-activated receptor-2. Collectively, upregulation of PDZK1 could have an important role in the development of melasma in connection with estrogen through NHE, CFTR, and SLC26A3.

Kim NH, Lee TR, PDZK1 upregulation in estrogen-related hyperpigmentation in melasma. Journal of Investigative Dermatology. 2012; 132:2622–2631

Jemds.com Original Article

STUDY OF HORMONAL PROFILE IN FEMALE MELASMA PATIENTS IN A TERTIARY CARE HOSPITAL

Kiran Kumre[1], Krishnendra Varma[2], Harsh Sharma[3], Ujjwal Singh[4]

ABSTRACT

BACKGROUND

Melasma is a chronic skin disorder that results in symmetrical, blotchy, brownish facial pigmentation.

AIM

To study the hormonal profile (T3, T4, TSH, Oestrogen, Progesterone, Prolactin) in female melasma patients.

OBJECTIVES

To study the hormonal profile (Sr. oestrogen, progesterone, prolactin, T3, T4 and TSH) and hormonal imbalance in female melasma patients attending Dermatology OPD of CRGH within 1 year by correlating with the normal levels.

MATERIALS AND METHODS

Sixty-six female patients suffering from melasma between the ages of 15-45 years were enrolled in the study. Patients were investigated for various hormone levels, i.e. T3, T4, TSH, Oestrogen, Progesterone, Prolactin at any time of their menstrual cycle and their values estimated according to Follicular (FP) and Luteal Phase (LP) values.

RESULTS

Amongst the sixty-six patients only 18 (27.3%) had normal values for oestrogen, while the remaining 48 patients (72.7%) had deranged values (Mostly increased). Out of 66 patients, progesterone level was normal in 28 (42.4%) and deranged in 38 (57.6%). Prolactin level was found normal in 59 (89.4%) and deranged in 7 (10.6%) of the patients. T3 level was found to be normal in 49 (74.2%), increased in 9 (13.6%) and decreased in 8 (12.1%) of the patients. T4 was found normal in 51 (77.3%), increased in 8 (12.1%) and decreased in 7 (10.6%) of the patients. TSH level was found normal in 43 (65.2%), increased in 18 (27.3%) and decreased in 5 (7.6%) of the patients.

CONCLUSION

It was concluded raised oestrogen and progesterone levels contribute towards the development of melasma. Hypothyroidism is found to be associated with melasma in many cases.

KEYWORDS

Melasma, Hypothyroidism, Oestrogen, Progesterone, Melanin Stimulating Hormone.

Kumre K, Varma K, Sharma H, Singh U. Study of hormonal profile in female melasma patients in a tertiary care hospital. J. Evolution Med. Dent. Sci. 2016; 5(31):1663-1667.

American Journal of Clinical and Experimental Medicine
Volume 4, Issue 2, March 2016, Pages: 26-29

Analysis Level of Serum Estradiol Hormone of Pregnant Women with Melasma

Andi Miranti[1], Anis Irawan Anwar[1], Khairuddin Djawad[1], Ilhamjaya Patellongi[2], Siswanto Wahab[1], Nusratuddin Abdullah[3]

[1]Department of Dermatology, Medical Faculty, Hasanuddin University, Makassar, South Sulawesi, Indonesia
[2]Faculty of Public Health, Hasanuddin University, Makassar, South Sulawesi, Indonesia
[3]Department of Obstetric and Ginecology, Medical Faculty, Hasanuddin University, Makassar, South Sulawesi, Indonesia

64 pregnant women (15-49 years old) who suffered from melasma in the third trimester and who did not, and the blood was drawn to measure the level of serum estradiol hormone. **Estradiol levels in women with melasma are higher than not melasma**

Miranti A, Anwar AI, Djawad K, Patellongi I, Wahab S, Abdullah N. Analysis level of serum estradiol hormone of pregnant women with melasma. American Journal of Clinical and Experimental Medicine. 2016;4(2):26-29.

J Clin Aesthet Dermatol. 2017 Feb; 10(2): 57–58
Published online 2017 Feb 1.
PMCID: PMC5367874

Melasma Associated with Topical Estrogen Cream

Alyson Snyder, DO,[a] Rachel A. Schiechert, MD,[b] and Martin N. Zaiac, MD[c]

Author information ▶ Copyright and License information ▶

Abstract

Go to

A 47-year-old woman presented with hyperpigmented patches on her upper extremities. The patient had begun using a topical estrogen cream in the affected areas prior to noticing the hyperpigmentation. A diagnosis of melasma secondary to topical estrogen cream was made. While systemic hormones are a well-documented trigger for the development of melasma, this case represents the first report of melasma associated with topical estrogens. Topical estrogens are frequently prescribed to postmenopausal women for skin rejuvenation. Melasma should be discussed as a potential side effect of systemic as well as topical estrogen preparations.

Anti estrogen?

Snyder A, Schiechert RA, Zaiac MN. Melasma associated with topical estrogen cream. J Clin Aesthet Dermatol. 2017;10(2):57–58.

Melasma treatment: A novel approach using a topical agent that contains an anti-estrogen and a vascular endothelial growth factor inhibitor

Philip R. Cohen *

Department of Dermatology, University of California San Diego, San Diego, CA, United States

ABSTRACT

Melasma is an acquired disorder of pigmentation that presents with asymptomatic symmetric darkening of the face. The pathogenesis of this condition is multifactorial and influenced by several factors including female sex hormones, genetic predisposition and ultraviolet light exposure. The management of melasma is usually directed at more than one of the causative etiologic factors and often incorporates a combination of topical agents, with or without the addition of physical modalities. Estrogen and angiogenesis are significant factors in the etiology of melasma. A useful addition to the therapeutic armentarium for treating melasma would include a topical agent that could effect both of these causative factors. Specifically, a topical preparation consisting of an anti-estrogen and a vascular endothelial growth factor inhibitor would accomplish this goal. Suitable candidates that target estrogen receptors and vascular endothelial growth factor are currently used in medical oncology as systemic antineoplastic agents. The anti-estrogen could be either a selective estrogen receptor modulator (such as tamoxifen or raloxifene) or an aromatase inhibitor (such as anastrozole or letrozole or exemestane). The vascular endothelial growth factor inhibitor would be bevacizumab. In conclusion, a novel-topically administered-therapy for melasma would combine an anti-estrogen and a vascular endothelial growth factor inhibitor.

Cohen PR. Melasma treatment: A novel approach using a topical agent that contains an anti-estrogen and a vascular endothelial growth factor inhibitor. Medical Hypotheses. 2017;1-5.

MELASMA AND THE PITUARY GLAND

- The intermediate lobe of the pituitary gland produces **melanocortins**, a class of peptide hormones crucial for melanogenesis which stimulate the production and release of melanin by melanocytes in skin and hair.
- The melanocortins include 3 different types of MSH (α-MSH, β-MSH, γ-MSH) and adrenocorticotropic hormone (ACTH), all derived from the same precursor, the proopiomelanocortin (POMC) prohormone, whose secretion is induced by corticotropin-releasing hormone (CRH) produced in the hypothalamus.
- In humans, **α-MSH and ACTH are also produced locally in the skin** (both in keratinocytes and melanocytes) and have a major role in pigmentation.

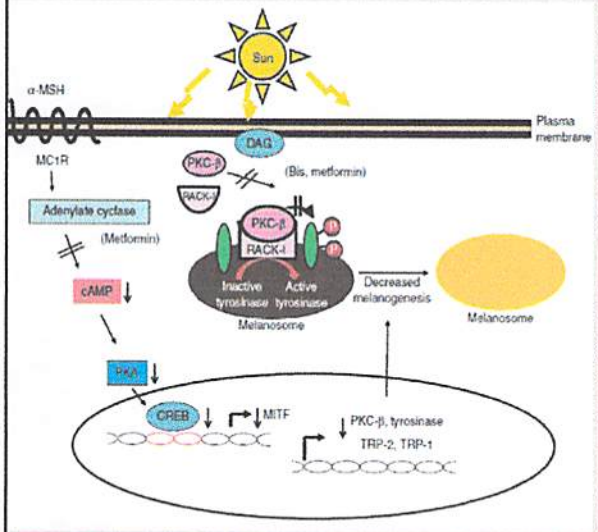
Muller I, Rees A. Melasma and endocrine disorders. Journal of Pigmentary Disorders. 2014;1:5.

- No association between melasma and pituitary disorders has been reported in the literature, although the role of melanocortins in melanogenesis is clear.
- Melasma does not involve circulating melanocortins produced by the pituitary gland but more likely those locally produced in the skin.

This hypothesis is supported by the work of Im et al. who found an increased expression of α-MSH in lesional melasma skin.

Im S, Kim J, On WY, Kang WH. Increased expression of alpha-melanocyte stimulating hormone in the lesional skin of melasma.

Metformin : A potential drug to treat hyperpigmentation disorders



Metformin is an antidiabetic drug. metformin was shown to decrease intracellular levels of cAMP. Because cAMP is a well-known modulator of melanin synthesis. **Metformin blocked foreskolin and a-melanocyte-stimulating hormone (a-MSH)**-induced increases in the levels of melanin.

Lehraiki A, Abbe P, Cerezo M et al. Inhibition of melanogenesis by the antidiabetic metformin. J Invest Dermatol. 2014;134:2589–97.

Metformin: A Potential Drug to Treat Hyperpigmentation Disorders

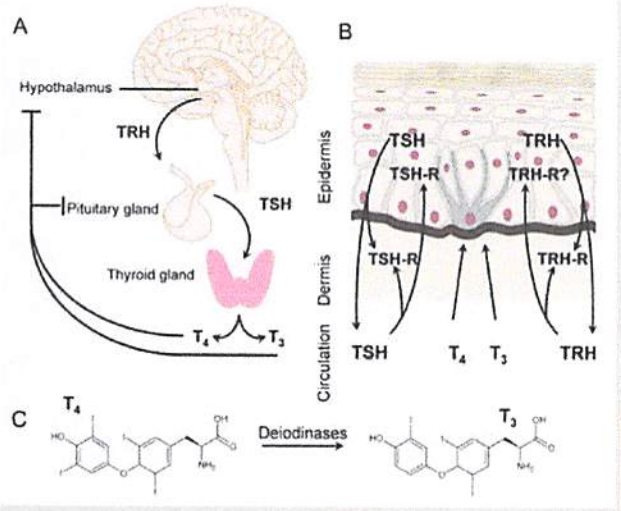
Elisabeth S. Belisle[1] and Hee-Young Park[1]

Hyperpigmentation disorders are generally difficult to treat because of the limited availability of effective therapeutics with minimal side effects. In this issue, Lehraiki *et al.* report that metformin, an antidiabetic drug, inhibited melanogenesis, *in vitro* and *in vivo*, and they suggest that metformin may be used to treat hyperpigmentation disorders. This commentary reviews the molecular mechanisms through which metformin inhibits melanogenesis and examines metformin as a potential drug to treat hyperpigmentation.

Journal of Investigative Dermatology (2014) 134, 2488–2491. doi:10.1038/jid.2014.245

Lehraiki A, Abbe P, Cerezo M et al. Inhibition of melanogenesis by the antidiabetic metformin. J Invest Dermatol. 2014;134:2589–97.

MELASMA AND THYROID HORMONES

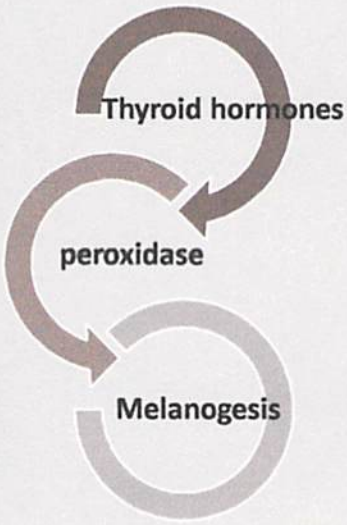


One of the hormones that controls for melanogenesis is the **thyroid hormone.**

Skin is a target of the thyroid hormone that plays an important role in **regulating epidermal homeostasis.**

Normal levels of hormones thyroid is necessary for efficient homeostasis, function and epidermal regeneration.

Mullet L, Rees A. Melasma and endocrine disorders. Journal of Pigmentary Disorders. 2014;1:5.



- Thyroid hormone works on melanogenesis because thyroid hormones stimulate epidermal oxygen consumption in the process of oxidation of melanogenesis through peroxidase.
- Peroxidase involvement in melanogenesis polymerization which can cause hyperpigmentation.

Çakmak SK, Özcan N, Kılıç N, Koparal S, Artüz F, Çakmak A, Kose K. Etiopathogenetic factors, thyroid functions and thyroid autoimmunity in melasma patients. Postep Derm Alergol 2015; XXXII (5): 327–330.

Postepy Dermatol Alergol. 2015 Oct; 32(5): 327–330. PMCID: PMC4692817
Published online 2015 Oct 29. doi: 10.5114/pdia.2015.54742

Etiopathogenetic factors, thyroid functions and thyroid autoimmunity in melasma patients

Seray Külcü Çakmak,[✉1] Nimet Özcan,[1] Arzu Kılıç,[1] Suha Koparal,[2] Ferda Artuz,[1] Atıl Çakmak,[3] and Kenan Kose[4]

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Abstract

Introduction: Melasma is a common chronic, acquired pigmentation disorder with a significant impact on the quality of life of patients.

Aim: To investigate the etiopathogenetic factors, thyroid functions and thyroid autoimmunity in patients with melasma.

Material and methods: Forty-five women with melasma and 45 age-matched healthy women were included in the study group. A detailed history was taken from the patients including triggering factors of melasma. Serum free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), anti-thyroglobulin (AbTG) and anti-thyroid peroxidase (Ab-TPO) were measured and thyroid ultrasonography was performed for each subject.

Results: In 26.7% of patients, pregnancy, in 17.8%, oral contraceptive use and in 13.3%, intense sunlight exposure were the triggering factors. 17.8% of patients had a family history of melasma. FT4, TSH and AbTG levels were significantly higher in the patient group.

Conclusions: The results suggest that a combination of factors including pregnancy, oral contraceptive use, sunlight and genetic factors often trigger melasma. Thyroid hormones and thyroid autoimmunity may also play a role in the pathogenesis which needs to be proven by further studies.

Key words: melasma, thyroid, etiopathogenesis.

Çakmak SK, Özcan N, Kılıç N, Koparal S, Artüz F, Çakmak A, Kose K. Etiopathogenetic factors, thyroid functions and thyroid autoimmunity in melasma patients. Postep Derm Alergol 2015; XXXII (5): 327–330.

Syarif FR (Padang, 2016)
(unpublished)

Correlation of triiodothyronine and thyroid stimulating hormone serum levels with the severity of melasma.

Thirty-six women with melasma aged >18 year. MASI score was recorded, TSH and T3 serum levels were measured.

Increased levels of T3 and TSH in accordance with the increased of severity degree of melasma.

Yenny SW
Padang, 2017
(Unpublished)

"Stress Relation Analysis with Triidothyronine (T3) and Thyroid-Stimulating Hormone (TSH) Serum in Melasma Patients"

Cross sectional study design in 45 patients with melasma. Patients were tested for serum T3 and TSH levels, a stress indicator by filling out a DASS (Depression Anxiety Stress Scale) questionnaire prior to the study.

T3 and TSH serum levels were higher in the stress group than in the normal group, but were not statistically significant.

Methimazole (1-methyl-2-mercaptoimidazole: MMI)

Antithyroid agent that has been orally used for the treatment of hyperthyroidism during the past 5 decades.

When used topically, MMI serves as an inhibitor of melanin production and produces skin depigmentation in laboratory animals and human subjects.

Both in thyroid cells and in melanocytes MMI accomplishes metabolization through the inhibition of peroxidase.

The peroxidase present in cutaneous melanocytes accomplishes the metabolization of several melanin intermediates.

Kasraee B, Ardekani GHS, Parhizgar A, Handjani F, Omrani GR, Samani M, et al.. Safety topical methimazole for the treatment of melasma. Skin Pharmacol Physiol. 2008; 21: 300-5.
Malek J, Chedraoui A, Nikolic D, Baroutt N, Ghosn S, Abbas O. Successful treatment of hydroquinone-resistant melasma using topical methimazole. Dermatologic Therapy. 2013; Vol.26: 69-72.

The inhibition of peroxidase by MMI could thus interfere with different steps in the biosynthesis of eumelanin and pheomelanin pigments

Some of these advantages include the non-cytotoxicity and non mutagenicity characteristics of MMI compared to hydroquinone.

Kasraee B, Ardekani GHS, Parhizgar A, Handjani F, Omrani GR, Samani M, et al.. Safety topical methimazole for the treatment of melasma. Skin Pharmacol Physiol. 2008; 21: 300-5.
Malek J, Chedraoui A, Nikolic D, Baroutt N, Ghosn S, Abbas O. Successful treatment of hydroquinone-resistant melasma using topical methimazole. Dermatologic Therapy. 2013; Vol.26: 69-72.

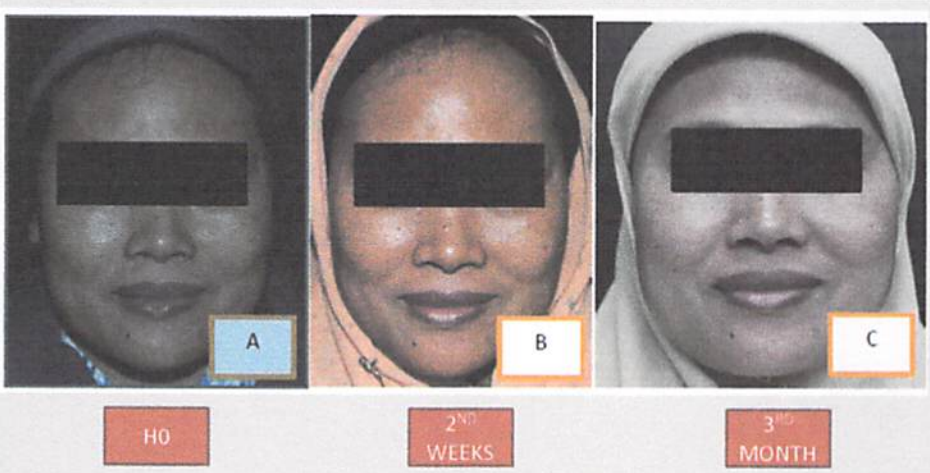
Murasmita A, et al (Solo)

Compare the efficacy of tranexamic acid and methimazole in combination with microneedling in melasma patients.

Split-face study with 7 sample subjects; 7 patients that met the inclusion criteria were given 1 mm needle-depth of microneedling , and given TA topical on right cheek, and methimazole on the left. Clinical images , Modified Melasma Area Severity Index (mMASI) scoring and Mexameter® analysis were performed.

Statistically significant decreased melanin index after the application of both TA ($p<0.002$) and methimazole ($p<0.013$).
No serious side effects were reported.

Murasmita A, Kusumawardani A. Perbandingan efek methimazole dan asam traneksamat kombinasi dengan microneedling sebagai terapi melasma: Studi pendahuluan.



Murasmita A, Kusumawardani A. Perbandingan efek methimazole dan asam traneksamat kombinasi dengan microneedling sebagai terapi melasma: Studi pendahuluan.

Kasraee B, et al. (Iran, 2018)

Skin Pharmacol Physiol. 2008;21(6):300-5. doi: 10.1159/000148222. Epub 2008 Jul 31.

Safety of topical methimazole for the treatment of melasma. Transdermal absorption, the effect on thyroid function and cutaneous adverse effects.

Kasraee B[1], Safaee Ardekani GH, Parhizgar A, Handjani F, Omrani GR, Samani M, Nikbakhsh M, Tanideh N, Eshraghian A, Sorg O, Saurat JH.

⊕ Author information

Abstract

Methimazole is an oral antithyroid compound that exhibits a skin-depigmenting effect when used topically. However, the effect of topical methimazole on thyroid function has not been reported. This study was aimed at assessing the safety of topical methimazole used to treat pigmented lesions, without affecting thyroid hormones due to systemic delivery. The pharmacokinetics of methimazole, either applied in the form of a 5% topical formulation to facial skin or taken orally in the form of a 5-mg tablet by 6 volunteers, were determined. In addition, the effect of long-term topical applications of 5% methimazole on the function of the thyroid gland in 20 patients with epidermal melasma was determined following 6 weeks of once-daily application. Cutaneous adverse effects of topical methimazole were determined. From 15 min up to 24 h after application, methimazole was undetectable in the serum of the individuals receiving single topical methimazole dosing. Methimazole, however, was detected in serum after 15 min of oral administration and remained detectable in serum up to 24 h after administration. Long-term topical methimazole applications in melasma patients did not induce any significant changes in serum TSH, free thyroxine and free triiodothyronine levels. Topical methimazole was well tolerated by the patients and did not induce any significant cutaneous side effects. Present data together with the previously shown non-cytotoxic and non-mutagenic characteristics of methimazole indicate that this agent could be considered as a safe skin-depigmenting compound for topical treatment of skin hyperpigmentary disorders in humans.

Kasraee B, Ardekani GHS, Parhizgar A, Handjani F, Omrani GR, Samani M, et al.. Safety topical methimazole for the treatment of melasma. Skin Pharmacol Physiol. 2008; 21: 300-5.

Dermatol Ther. 2013 Jan-Feb;26(1):69-72. doi: 10.1111/j.1529-8019.2012.01540.x.

Successful treatment of hydroquinone-resistant melasma using topical methimazole.

Malek J[1], Chedraoui A, Nikolic D, Baroutt N, Ghosn S, Abbas O.

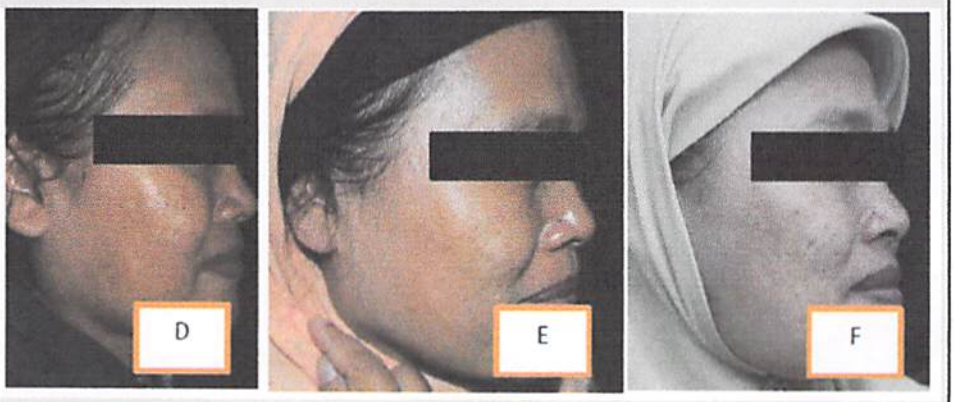
⊖ Author information

1 Dermatology Department, American University of Beirut Medical Center, Beirut, Lebanon.

Abstract

Melasma is an acquired hyperpigmentation skin disorder in sun-exposed areas. It occurs almost exclusively over the face, and is most commonly seen in women. Several depigmenting agents have been used for the treatment of melasma among which hydroquinone has been the most widely used due to its efficacy and safety in short-term use. However, hydroquinone is recently reported to be a cytotoxic and mutagenic compound in mammalian cells and is thus banned in several countries. Hydroquinone ban has caused investigators to search for alternative depigmenting agents for the treatment of melasma in recent years. Methimazole is an antithyroid agent orally used in humans since several decades and has been shown that when applied topically, it inhibits melanin synthesis and causes skin depigmentation in lab animals as well as human subjects. Herein, we report two hydroquinone-resistant melasma patients who were successfully treated with methimazole cream. Application of 5% methimazole cream once daily resulted in significant improvement of melasma in both patients after 8 weeks. The efficacy of methimazole for melasma treatment as well as its advantages over other known depigmenting compounds (non-mutagenicity, non-cytotoxicity and high tolerability profile) suggests that topical methimazole should be added to the armamentarium of anti-melasma treatment.

Malek J, Chedraoui A, Nikolic D, Baroutt N, Ghosn S, Abbas O. Successful treatment of hydroquinone-resistant melasma using topical methimazole. Dermatologic therapy. 2013; Vol.26: 69-72.



Murasmita A, Kusumawardani A. Perbandingan efek methimazole dan asam traneksamat kombinasi dengan microneedling sebagai terapi melasma: Studi pendahuluan.

Yenny SW
Padang, 2017
(Unpublished)

"The comparison on the use of 5% methimazole cream with 4% kojic acid in melasma therapy"

Assessing the effectiveness, patient satisfaction, and adverse-effects of 5% methimazole cream with 4% kojic acid in melasma therapy.

A single-blind research of 45 patients with melasma, comparing randomized right-left (split face).

Result

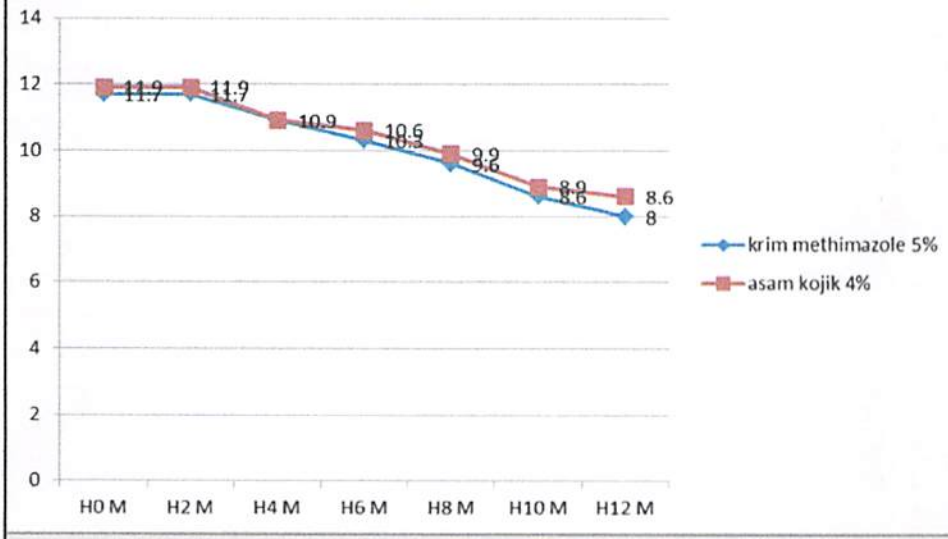


Diagram of right and left facial MASI changes at each visit

Result

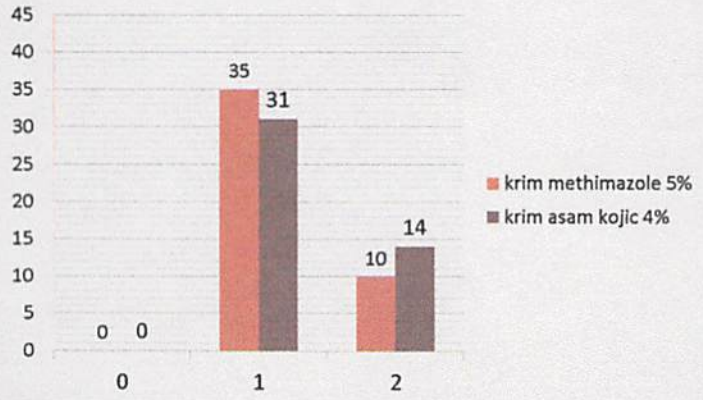
Treatment	n	MASI Ho-H12	p value
Methimazole 5%	45	3,7 ± 2,4	0,299
Kojic acid 4%	45	3,2 ± 1,9	

The difference on the MASI reduction on right and left face

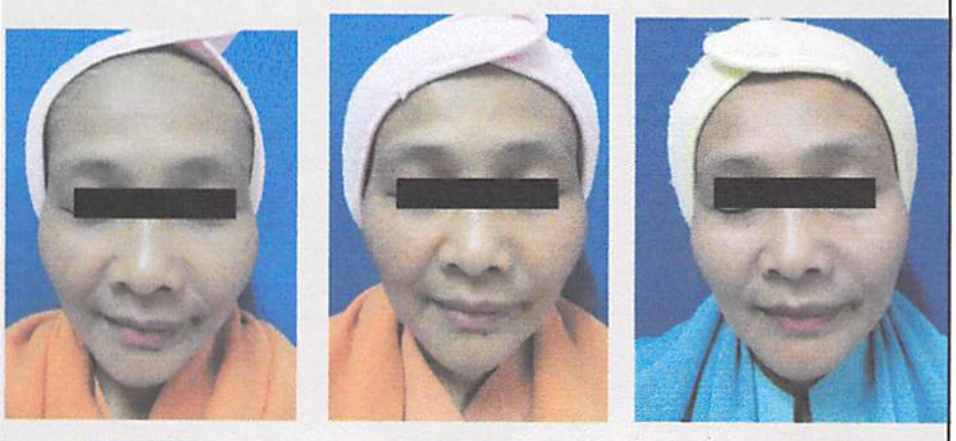
Treatment	n	Pigment Ho-H12	p value
Methimazole 5%	45	7,12 ± 4,1	0,755
Kojic acid 4%	45	7,5 ± 4,2	

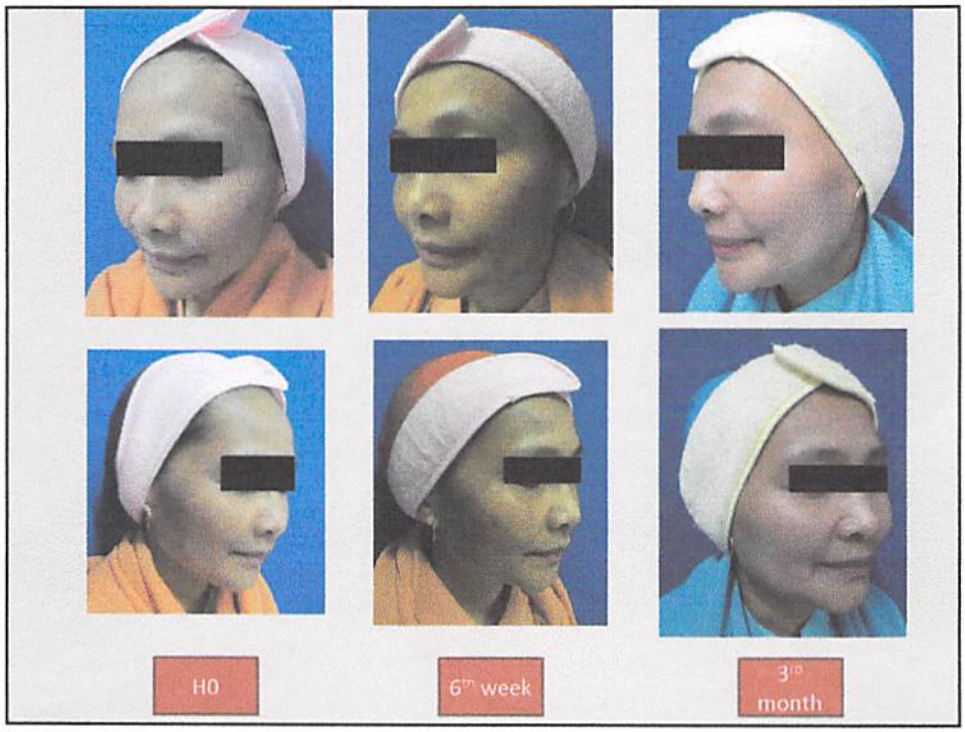
The difference of pigment reduction of index of mexameter on the right and left face.

Result



The comparison of patient's satisfaction on the use of 5% methimazole cream and 4% kojic acid after research.





Take home messages

- A novel–topically administered–double therapy for melasma would combine an anti-estrogen and a vascular endothelial growth factor inhibitor.
- Metformin has effects on key melanogenic proteins and signaling pathways. Metformin is a potential therapeutic agent to treat hyperpigmentation disorders.
- Further research is needed to know methimazole 5% cream as an alternative therapy of melasma.

THANK YOU