A Study to Assess the Relationship between Melasma and Thyroid Autoimmunity

Thesis

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List of contents

List of figures

List of tables

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Introduction

Melasma is a common disorder of hyperpigmentation affecting millions of people worldwide (***Sheth and Pandya, 2011*-a**).The exact cause of melasma is unknown, the majority of cases are attributed to pregnancy, combined oral contraceptive pills (OCPs), genetic factors, sun exposure, use of cosmetic products, thyroid disorders and anticonvulsant drugs (***Grimes, 1995)***.

Melasma is often difficult to treat, which has a significant impact on patients' quality of life. It is found most commonly in women with Fitzpatrick skin phototypes IV through VI living in areas of intense ultraviolet light exposure (***Freitag et al., 2008***).

There are three major patterns of distribution of the lesions. Centrofacial melasma is the commonest (63%) and affects the forehead, nose, chin and upper lips. The Malar type comes next (21%) and is distributed over the nose and cheeks. The third type is the Mandibular (16%) and it overlies the mandibular ramus (***Mandry-Pagan and Sanchez, 2000***).

Cutaneous manifestations of thyroid disorders can be classified into two main groups. The first group includes cutaneous diseases in relation to thyroid disorders, especially thyroid autoimmunity such as vitiligo, idiopathic hirsutism, bullous diseases and melasma. The second group includes cutaneous manifestations of thyroid disorders such as myxedema, xanthoma, intraepidermal blisters and hyperhydrosis (***Niepomniszcze and Amad, 2001***).

A study in 1985 found an association between thyroid autoimmunity and melasma, mostly in women whose melasma developed during pregnancy or after ingestion of OCPs. In addition, patients with melasma were 4 times more likely to have thyroid abnormalities than age-and sex-matched controls (***Lutfi et al., 1985***).

In accordance with this, another Iranian study in 2006 revealed a possible relationship between thyroid autoimmunity and melasma where thyroid disorders were reported to be 3.4 times more prevalent in patients than controls ***(Kiani et al., 2006)***. Recently a study was made for the same purpose, but the results were doubtful about the association of melasma and thyroid disorders (***Yazdanfar and Hashemi, 2010***).

Aim of work

The current study aimed to evaluate the relationship between melasma and autoimmune thyroid disorders.

Melasma

Facial appearance plays a major role in self perception and interaction with others and severe facial blemishes like melasma leave a significant impact on a woman's quality of life ***(Balkrishnan et al., 2006).***

Melasma is an acquired hypermelanosis occurring symmetrically on sun-exposed areas of the body. Although no sex, age or race is exempt, it is more common in women of Hispanic, Asian, African and Middle Eastern descent ***(Victor et al., 2004).*** Melasma is however rare before puberty, it occurs most commonly in females during their reproductive years. Exacerbating factors include pregnancy, oral contraception and sun exposure. The exact cause of melasma is still somehow mysterious (***Sheth and Pandya, 2011-a).***

1. Melanogenesis

Melanogenesis is a process by which melanin pigment is synthesized and deposited by the means of melanocytes and their specialized organelles; melanosomes ***(Prota, 2000).***

- ***Melanocytes:***

Melanocytes are dendritic cells derived from melanoblasts during the first 2 months of fetal development ***(Kovacs, 1998),*** situated among keratinocytes at the basal epidermal layer. They

are found in places other than skin and hair such as mucous membranes, nervous system, uveal tract, pigmented epithelium, inner ear and cochlea ***(Witkop, 1983).***

Each melanocyte provides melanin to 36 neighboring keratinocytes (melanin unit). They synthesize melanin out of tyrosine amino acid by the coactions of melanocytic tyrosinase enzymes TRP1 and TRP2 and the action of lysosomal proteins LAMP ***(Setaluri, 2003).***Three variants of melanin are produced:

- Eumelanin: black-brownish colored.
- Pheomelanin: yellow-reddish colored.
- Neuromelanin: black colored, present in nerve cells ***(Nieuwpoort et al., 2004)***

Eumelanin is synthesized through acting on tyrosine to be converted to DOPA and DOPA quinone, further cyclisation of DOPA produces cyclo-DOPA and DOPA chrome. And with the action of TRP, Dihydrochinindol-2-carboxyl acid (DHICA) is produced, which is further oxidized to produce eumelanin ***(Aubin and Mousson, 2004).***

Pheomelanin is produced in smaller amount than eumelanin, it is the product of nucleophilic oxidation of L-cystiene in presence of DOPA quinone ***(Eller et al., 1994).***

- ***Factors affecting melanogenesis:***

1. Hormones:

•Hormones stimulating melanogenesis include; melanocortins (MSH), adrenocorticotropic hormones (ACTH), β-endorphins,

opioids, endothelins, histamines, eicosaniods, catecholamines, estrogen and androgens.

- Hormones inhibiting melanogenesis include; serotonin, dopamine, acetylcholine, melanocortins antagonist and glucocorticoids (***Slominski et al., 2004***).

2.Vitamins: vitamin D and A may stimulate melanogenesis while vitamin E (tocopherols) may exert an inhibitory effect on melanin synthesis (***Raposo et al., 2001***).

3.Stem cell factor (SCF): also known as mast cell growth factor or c-kit ligand, expressed in various cell types including melanocytes. SCF binding not only activates receptor kinase activity but also turns c-kit into a phosphorylation substrate via creation of tyrosine phosphorylated receptors docking sites on c-kit. Signaling by c-kit may also favor melanocyte proliferation (***Sharov et al., 2003***).

4.Ultraviolet light exposure: is the stimulant for melanogenesis along with some endocrinal diseases that may also cause abnormal melanogenesis. In addition to that, UVR also enhances the differentiation of melanocytes in skin through the increase of tyrosinase and TRP1 activity without any increase in their concentration ***(Kruger-Krasagakes et al., 1995)***.

5.Cytokines and Growth factors: Interleukin (IL)-1 and 6, interferon (IFN)-α and γ, Tumor necrosis factor (TNF) α and β

and Tumor growth factor (TGF) β1, stimulate melanogenesis ***(Smith et al., 1993).***

2. Prevalence of Melasma:

Melasma comes from the Greek melas meaning black. It is also called chloasma or mask of pregnancy, chloasma is derived from a Greek word meaning green, and because skin pigmentation is never green the term melasma is the preferred one ***(Montemarano et al., 2011).***

Melasma is the most common pigmentary disease during pregnancy, more than 50 % of pregnant women experience melasma ***(Werlinger et al., 2007)***. The condition is most commonly seen on the face of women with Fitzpatrick types IV to VI living in areas of intense ultraviolet (UV) light ***(Freitag et al., 2008)***.

3. Melasma in Males:

Melasma appears less commonly in men, with prevalence 14 % - 25%. The main causes of melasma in men are sun exposure and family history; it is also more common in Indian men; however it shares the same clinicohistopatholgical features of melasma in women ***(Vachiramon et al., 2012.)*** A complete hormonal profile was done for ten males with melasma, it was reported that the circulating luteinizing hormone (LH) was higher in melasma men and testosterone level was lower, compared to their counterpart controls ***(Sialy et al., 2000).***

4. Etiopathogenesis:

Although the exact etiology of melasma is still unknown, studies have shown that the underlying basis of melasma may be more complex than originally thought ***(Sheth and Pandya, 2011-a)***.

4.1. Genetic:

Melasma was found in high incidence among family members, 48% of 324 women in a global survey reported a family history of melasma ***(Ortonne et al., 2009)***. Another Iranian survey of pregnant women with melasma reported 54.7% incidence of melasma in family members, which strongly suggests genetic predisposition ***(Moin et al., 2006)***.

4.2. Ultraviolet light:

Ultraviolet light is a common initiating or exacerbating factor for melasma, probably due to its effect on melanocytic proliferation, migration and melanogenesis owing to its effect on many cytokines production including interleukin-1 (IL-1), endothelin-1, α-MSH and adrenocorticotropic hormone (ACTH) from keratinocytes leading to up regulation of melanocytic proliferation and melanogenesis ***(Im et al., 2007)***.

4.3. Hormonal:

A study by Lieberman and Moy in 2008 revealed that estrogen receptor expression is increased in melasma affected skin compared to perilesional normal skin ***(Lieberman and Moy,***

2008). A preceeding study by Perez et al examined the link between circulating levels of hormones and their relationship to melasma; they found that nulligravid women with melasma had significantly higher serum levels of LH and lower levels of estradiol than their counterpart controls ***(Perez et al., 1983)***.

4.4. Oral contraceptive pills:

Several authors tried to find out an evidential link between the OCPs intake and melasma. Resnick found this link in a study made upon 212 female patients, as he found that 29 % of patients directly developed melasma after using OCPs, 87% of them also developed melasma after pregnancy ***(Resnick, 1967)***. Moreover, Ortonne el al found that 25 % of 324 women being treated for melasma reported the initial onset of the disease with the use of OCPs ***(Ortonne et al., 2009)***.

4.5. Thyroid disorders:

In 1985, while evaluating thyroid hormone levels in Argentinean females with melasma developing during pregnancy or after using OCPs , Lutfi and his colleagues found a 70 % incidence of mild thyroid abnormalities compared to 39.4 % with idiopathic melasma ***(Lutfi et al., 1985)***. Another two Iranian studies were made in 2006 and 2010 consecutively; first Kiani et al found that 37.8 % of his melasma patients and 11.1 % of the controls had thyroid disorders, concluding that there is a significant relationship between melasma and thyroid disorders especially hypothyroidism and thyroid autoimmunity ***(Kiani et al., 2006)***. In the second study, it was reported that, despite the

higher values of anti TPO antibodies, free T_3 and TSH, no significant difference was obtained in the mean serum levels of these parameters between melasma patients and the control group, which puts some doubt on the association of melasma and thyroid autoimmunity ***(Yazdanfar and Hashemi, 2010)***.

4.6. Vascular endothelial growth factor (VEGF):

Kim and his colleagues examined the expression of VEGF protein using immunohistochemistry, lesional skin showed positive immunoreactivity against VEGF in keratinocytes compared to nonlesional neighboring skin. Based on that, it was concluded that there is an increase in the number and size of blood vessels in skin of melasma patients. Moreover it is noticed that the increase in the number of blood vessels is more than the increase in size of the vessels ***(Kim et al., 2007)***.

4.7. Nerve growth factor receptor:

Through obtaining biopsy specimens of both lesional and non lesional skin in six Asian females with melasma , Bak el al stained the biopsies for nerve growth factor receptor (NFGR) and there was an increased number of keratinocytes expressing NFGR and more hypertrophic nerve fibers in the superficial dermis of lesional compared to nonlesional skin ***(Bak et al., 2009)***.

4.8. Stem cell factor:

On studying stem cell factor expression on melasma affected skin, an overexpression was detected in dermal layers of lesional